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(71) Applicants (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). THE MONSANTO COMPANY [US/US]; 800 North Lindbergh Boulevard, St. Louis, MO 63167 (US).

(72) Inventors; and
(75) Inventors/Applicants (for US only): VAZQUEZ, Michael, L. [US/US]; 233 Saratoga Court, Gurnee, IL 60031 (US).

MUELLER, Richard, A. [US/US]; 562 Stonegate Terrace, Glencoe, IL 60022 (US). TALLEY, John, J. [US/US]; 8772 Pine Avenue, Brentwood, MO 63144 (US). GETMAN, Daniel, P. [US/US]; 66 Sunny Hill Court, Chesterfield, MO 63017 (US). DECRESCENZO, Gary, A. [US/US]; 536 Schrader Farm Drive, St. Peters, MO 63376 (US). FRESKOS, John, N. [US/US]; 7572 York, Clayton, MO 63105 (US). BERTENSHAW, Deborah, E. [US/US]; 8758 Pine Avenue, Brentwood, MO 63144 (US). HEINTZ, Robert, M. [US/US]; 603 Nancy Place, Ballwin, MO 63021 (US).

(74) Agents: UNGEMACH, Frank, S. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).

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(54) Title: HYDROXYETHYLAMINO SULPHONAMIDES USEFUL AS RETROVIRAL PROTEASE INHIBITORS

(57) Abstract

Hydroxyethylamino sulphonamide compounds of formulae (1) and (2), wherein A, R^2, R^3, R^4, R^6, x, P^1 and P^2 are as defined in claims 1 and 8 are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease.

(1)

(2)

1

Hydroxyethylamino sulphonamides useful as retroviral protease inhibitors

RELATED APPLICATION

5   This application is a continuation in part
application of co-owned and co-pending U.S. patent
application Serial No. 08/204,827 filed March 2, 1994,
which is a continuation in part application of co-owned
and co-pending PCT/US93/07814, filed August 24, 1993,
10   which is a continuation in part application of co-owned
U.S. patent application Serial No. 07/934,984 filed
August 25, 1992, now abandoned, each of which is
incorporated herein by reference in its entirety.

15   **BACKGROUND OF THE INVENTION**

1. Field of the Invention
          The present invention relates to retroviral
protease inhibitors and, more particularly, relates to
20   novel compounds and a composition and method for
inhibiting retroviral proteases. This invention, in
particular, relates to sulfonamide-containing
hydroxyethylamine protease inhibitor compounds, a
composition and method for inhibiting retroviral
25   proteases such as human immunodeficiency virus (HIV)
protease and for treating a retroviral infection, e.g.,
an HIV infection. The subject invention also relates to
processes for making such compounds as well as to
intermediates useful in such processes.
30

2. Related Art
          During the replication cycle of retroviruses,
gag and gag-pol gene transcription products are translated
as proteins. These proteins are subsequently processed by
35   a virally encoded protease (or proteinase) to yield viral
enzymes and structural proteins of the virus core. Most
commonly, the gag precursor proteins are processed into

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the core proteins and the pol precursor proteins are
processed into the viral enzymes, e.g., reverse
transcriptase and retroviral protease. It has been shown
that correct processing of the precursor proteins by the
5   retroviral protease is necessary for assembly of
infectious virons. For example, it has been shown that
frameshift mutations in the protease region of the pol
gene of HIV prevents processing of the gag precursor
protein. It has also been shown through site-directed
10   mutagenesis of an aspartic acid residue in the HIV
protease active site that processing of the gag precursor
protein is prevented. Thus, attempts have been made to
inhibit viral replication by inhibiting the action of
retroviral proteases.
15

Retroviral protease inhibition typically
involves a transition-state mimetic whereby the retroviral
protease is exposed to a mimetic compound which binds
(typically in a reversible manner) to the enzyme in
20   competition with the gag and gag-pol proteins to thereby
inhibit specific processing of structural proteins and the
release of retroviral protease itself. In this manner,
retroviral replication proteases can be effectively
inhibited.
25

Several classes of compounds have been
proposed, particularly for inhibition of proteases, such
as for inhibition of HIV protease. Such compounds
include hydroxyethylamine isosteres and reduced amide
30   isosteres. See, for example, EP O 346 847; EP O 342,541;
Roberts et al, "Rational Design of Peptide-Based
Proteinase Inhibitors, "Science, 248, 358   (1990); and
Erickson et al, "Design Activity, and 2.8Å Crystal
Structure of a C_2 Symmetric Inhibitor Complexed to HIV-1
35   Protease," Science, 249, 527 (1990).

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Several classes of compounds are known to be
useful as inhibitors of the proteolytic enzyme renin.
See, for example, U.S. No. 4,599,198; U.K. 2,184,730;
G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR
5   H725. Of these, G.B. 2,200,115, GB 2,209,752, EP O
264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-
containing hydroxyethylamine renin inhibitors. EP 468
641 discloses renin inhibitors and intermediates for the
preparation of the inhibitors, which include sulfonamide-
10   containing hydroxyethylamine compounds, such as 3-(t-
butoxycarbonyl)amino-cyclohexyl-1-(phenylsulfonyl)amino-
2(5)-butanol. G.B. 2,200,115 also discloses sulfamoyl-
containing hydroxyethylamine renin inhibitors, and EP
0264 795 discloses certain sulfonamide-containing
15   hydroxyethylamine renin inhibitors. However, it is known
that, although renin and HIV proteases are both
classified as aspartyl proteases, compounds which are
effective renin inhibitors generally cannot be predicted
to be effective HIV protease inhibitors.
20

BRIEF DESCRIPTION OF THE INVENTION

The present invention is directed to virus
25   inhibiting compounds and compositions. More
particularly, the present invention is directed to
retroviral protease inhibiting compounds and
compositions, to a method of inhibiting retroviral
proteases, to processes for preparing the compounds and
30   to intermediates useful in such processes. The subject
compounds are characterized as sulfonamide-containing
hydroxyethylamine inhibitor compounds.

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DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there
is provided a retroviral protease inhibiting compound of
5   the formula:

(I)
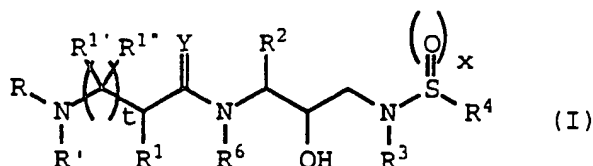
or a pharmaceutically acceptable salt, prodrug or ester
10   thereof, wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
alkylcarbonyl, cycloalkylcarbonyl,
cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl,
15   aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
aryloxyalkanoyl, heterocyclylcarbonyl,
heterocyclyloxycarbonyl, heterocyclylalkanoyl,
heterocyclylalkoxycarbonyl, heteroaralkanoyl,
heteroaralkoxycarbonyl, heteroaryloxycarbonyl,
20   heteroaroyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl,
aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl,
aminocarbonyl, aminoalkanoyl, and mono- and disubstituted
aminocarbonyl and mono- and disubstituted aminoalkanoyl
radicals wherein the substituents are selected from
25   alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
heteroaryl, heteroaralkyl, heterocycloalkyl,
heterocycloalkyalkyl radicals, or where said
aminocarbonyl and aminoalkanoyl radicals are
disubstituted, said substituents along with the nitrogen
30   atom to which they are attached form a heterocycloalkyl
or heteroaryl radical;

R' represents hydrogen, radicals as defined for R^3 or
$R''SO_2$- wherein R'' represents radicals as defined for R^3;

or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radicals;

5 R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine

10 and the sulfoxide (SO) and sulfone (SO$_2$) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, allo-threonine, serine, O-alkyl serine, aspartic acid, beta-cyano alanine and

15 valine side chains;

$R^{1'}$ and $R^{1"}$ independently represent hydrogen and radicals as defined for R^1, or one of $R^{1'}$ and $R^{1"}$, together with R^1 and the carbon atoms to which R^1, $R^{1'}$ and $R^{1"}$ are

20 attached, represent a cycloalkyl radical;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen

25 radials, $-NO_2$, $-CN$, $-CF_3$, $-OR^9$ and $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals, and halogen radicals;

R^3 represents hydrogen, alkyl, haloalkyl, alkenyl,

30 alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from

35 alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a

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disubstituted aminoalkyl radical, said substituents along
with the nitrogen atom to which they are attached, form a
heterocycloalkyl or a heteroaryl radical;

5   R^4 represents radicals as defined by R^3 except for
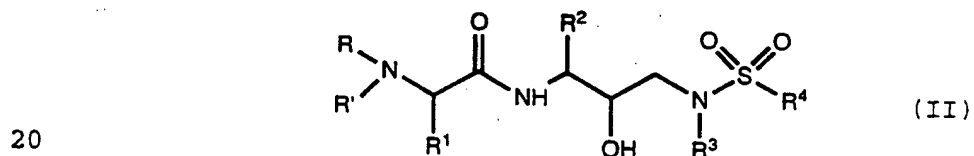   hydrogen;

    R^6 represents hydrogen and alkyl radicals;

10 x represents 0, 1 or 2;

    t represents either 0 or 1; and

    Y represents O, S and NR^{15} wherein R^{15} represents
15 hydrogen and radicals as defined for R^3.

        A family of compounds of particular interest
    within Formula I are compounds embraced by Formula II:

20

    wherein:

    R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
25 alkylcarbonyl, cycloalkylcarbonyl,
    cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl,
    aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
    aryloxyalkanoyl, heterocyclylcarbonyl,
    heterocyclyloxycarbonyl, heterocyclylalkanoyl,
30 heterocyclylalkoxycarbonyl, heteroaralkanoyl,
    heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
    heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl,
    aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl,
    aminocarbonyl, aminoalkanoyl, and mono- and disubstituted

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aminocarbonyl and mono- and disubstituted aminoalkanoyl
radicals wherein the substituents are selected from
alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
heteroaryl, heteroaralkyl, heterocycloalkyl,
5   heterocycloalkyalkyl radicals, or where said
aminoalkanoyl radical is disubstituted, said substituents
along with the nitrogen atom to which they are attached
form a heterocycloalkyl or heteroaryl radical;

10 R' represents hydrogen and radicals as defined for R^3 or
R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;

15 R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$,
$-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$,
$-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl,
alkenyl, alkynyl and cycloalkyl radicals, and amino acid
side chains selected from asparagine, S-methyl cysteine
20 and the sulfoxide (SO) and sulfone (SO_2) derivatives
thereof, isoleucine, allo-isoleucine, alanine, leucine,
tert-leucine, phenylalanine, ornithine, histidine,
norleucine, glutamine, threonine, allo-threonine, serine,
O-methyl serine, aspartic acid, beta-cyano alanine and
25 valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl
and aralkyl radicals, which radicals are optionally
substituted with a group selected from alkyl and halogen
30 radials, $-NO_2$, $-C \equiv N$, CF_3, $-OR^9$, $-SR^9$, wherein R^9
represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl,
hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
35 heterocycloalkyl, heteroaryl, heterocycloalkylalkyl,
aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and
disubstituted aminoalkyl radicals, wherein said

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substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said
5   substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

R^4 represents radicals as defined by R^3.
10

       A more preferred family of compounds within Formula II consists of compounds wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
15   alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl,
20   heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted
25   aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said
30   aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or
35   R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

9

R^1 represents $CH_2C(O)NHCH_3$, $C(CH_3)_2(SCH_3)$,
$C(CH_3)_2(S[O]CH_3)$, $C(CH_3)_2(S[O]_2CH_3)$, alkyl, alkenyl and
alkynyl radicals, and amino acid side chains selected
5   from the group consisting of asparagine, valine,
threonine, allo-threonine, isoleucine, tert-leucine,
S-methyl cysteine and the sulfone and sulfoxide
derivatives thereof, alanine, and allo-isoleucine;

10   R^2 represents alkyl, cycloalkylalkyl and aralkyl
radicals, which radicals are optionally substituted with
halogen radicals and radicals represented by the formula
$-OR^9$ and $-SR^9$ wherein R^9 represents alkyl radicals; and

15   R^3 and R^4 independently represent alkyl, alkenyl,
alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl
and heteroaralkyl radicals.

20   Of highest interest are compounds within
Formula II wherein

R represents alkoxycarbonyl, aralkoxycarbonyl,
alkylcarbonyl, cycloalkylcarbonyl,
25   cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl,
aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
aryloxyalkanoyl, heterocyclylcarbonyl,
heterocyclyloxycarbonyl, heterocyclylalkanoyl,
heterocyclylalkoxycarbonyl, heteroaralkanoyl,
30   heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and
disubstituted aminocarbonyl and mono- and disubstituted
aminoalkanoyl radicals wherein the substituents are
selected from alkyl, aryl, aralkyl, cycloalkyl,
35   cycloalkylalkyl, heteroaryl, heteroaralkyl,
heterocycloalkyl, heterocycloalkyalkyl radicals, or where
said aminoalkanoyl radical is disubstituted, said

10

substituents along with the nitrogen atom to which they
are attached form a heterocycloalkyl or heteroaryl
radical;

5   R' represents hydrogen and radicals as defined for R^3 or
R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;

10   R^1 represents $CH_2C(O)NHCH_3$, $C(CH_3)_2(SCH_3)$,
$C(CH_3)_2(S[O]CH_3)$, $C(CH_3)_2(S[O]_2CH_3)$, methyl, propargyl,
t-butyl, isopropyl and sec-butyl radicals, and amino acid
side chains selected from the group consisting of
asparagine, valine, S-methyl cysteine, allo-iso-leucine,
15   iso-leucine, and beta-cyano alanine side chains;

R^2 represents $CH_3SCH_2CH_2-$, iso-butyl, n-butyl, benzyl,
4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl
radicals;

20

R^3 represents isoamyl, n-butyl, isobutyl and cyclohexyl
radicals; and

R^4 represents phenyl, substituted phenyl and methyl
25   radicals.

          Another family of compounds of particular
interest within Formula I are compounds embraced by
Formula III:

30

(III)

wherein:
R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
35   alkylcarbonyl, cycloalkylcarbonyl,

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cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl,
aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
aryloxyalkanoyl, heterocyclylcarbonyl,
heterocyclyloxycarbonyl, heterocyclylalkanoyl,
5 heterocyclylalkoxycarbonyl, heteroaralkanoyl,
heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl,
aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl,
aminocarbonyl, aminoalkanoyl, and mono- and disubstituted
10 aminocarbonyl and mono- and disubstituted aminoalkanoyl
radicals wherein the substituents are selected from
alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
heteroaryl, heteroaralkyl, heterocycloalkyl,
heterocycloalkyalkyl radicals, or where said
15 aminoalkanoyl radical is disubstituted, said substituents
along with the nitrogen atom to which they are attached
form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or
20 R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$,
25 $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$,
$-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl,
alkenyl, alkynyl and cycloalkyl radicals, and amino acid
side chains selected from asparagine, S-methyl cysteine
and the sulfoxide (SO) and sulfone (SO_2) derivatives
30 thereof, isoleucine, allo-isoleucine, alanine, leucine,
tert-leucine, phenylalanine, ornithine, histidine,
norleucine, glutamine, threonine, allo-threonine, serine,
aspartic acid, beta-cyano alanine and valine side
chains;
35

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl
and aralkyl radicals, which radicals are optionally

12

substituted with a group selected from alkyl and halogen radicals, $-NO_2$, $-C\equiv N$, CF_3, $-OR^9$, $-SR^9$, wherein R^9 represents hydrogen and alkyl;

5   R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said
10 substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they
15 are attached, form a heterocycloalkyl or a heteroaryl radical; and

    R^4 represents radicals as defined by R^3.

20   A more preferred family of compounds within Formula III consists of compounds wherein

    R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl,
25 cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl,
30 heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl
35 radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl,

13

heterocycloalkyalkyl radicals, or where said
aminoalkanoyl radical is disubstituted, said substituents
along with the nitrogen atom to which they are attached
form a heterocycloalkyl or heteroaryl radical;

5

R' represents hydrogen and radicals as defined for R^3 or
R and R' together with the nitrogen to which they are
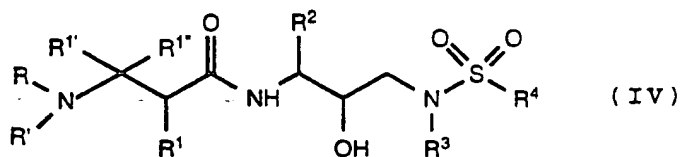attached represent heterocycloalkyl and heteroaryl
radical;

10

R^1 represents hydrogen, alkyl and alkenyl radicals, and
amino acid side chains selected from the group consisting
of asparagine, valine, threonine, allo-threonine,
isoleucine, tert-leucine, S-methyl cysteine and the
15   sulfone and sulfoxide derivatives thereof, alanine, and
allo-isoleucine;

R^2 represents alkyl, cycloalkylalkyl and aralkyl
radicals, which radicals are optionally substituted with
20   halogen radicals and radicals represented by the formula
$-OR^9$ and $-SR^9$ wherein R^9 represents hydrogen and alkyl
and halogen radicals; and

R^3 and R^4 independently represent alkyl, alkenyl,
25   alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl,
heteroaryl and heteroaralkyl radicals.

Of highest interest are compounds within
30   Formula III wherein

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
alkylcarbonyl, cycloalkylcarbonyl,
cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl,
35   aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
aryloxyalkanoyl, heterocyclylcarbonyl,
heterocyclyloxycarbonyl, heterocyclylalkanoyl,

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heterocyclylalkoxycarbonyl, heteroaralkanoyl,
heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and
disubstituted aminocarbonyl and mono- and disubstituted
5   aminoalkanoyl radicals wherein the substituents are
selected from alkyl, aryl, aralkyl, cycloalkyl,
cycloalkylalkyl, heteroaryl, heteroaralkyl,
heterocycloalkyl, heterocycloalkyalkyl radicals, or where
said aminoalkanoyl radical is disubstituted, said
10 substituents along with the nitrogen atom to which they
are attached form a heterocycloalkyl or heteroaryl
radical;

R' represents hydrogen and radicals as defined for R^3 or
15 R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;

R^1 represents hydrogen, methyl, propargyl, t-butyl,
20 isopropyl and sec-butyl radicals, and amino acid side
chains selected from the group consisting of asparagine,
valine, S-methyl cysteine, allo-iso-leucine, iso-leucine,
threonine, serine, aspartic acid, beta-cyano alanine, and
allo-threonine side chains;

25

R^2 represents $CH_3SCH_2CH_2-$, iso-butyl, n-butyl, benzyl,
4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl
radicals; and

30 R^3 represents alkyl, cyclohexyl, isobutyl, isoamyl, and
n-butyl radicals; and

R^4 represents methyl, phenyl and substituted phenyl
radicals wherein the substituents are selected from halo,
35 alkoxy, hydroxy, nitro and amino substituents.

15

Another family of compounds of particular
interest within Formula I are compounds embraced by
Formula IV:

(IV)

5

wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
alkylcarbonyl, cycloalkylcarbonyl,

10 cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl,
aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
aryloxyalkanoyl, heterocyclylcarbonyl,
heterocyclyloxycarbonyl, heterocyclylalkanoyl,
heterocyclylalkoxycarbonyl, heteroaralkanoyl,

15 heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl,
aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl,
aminocarbonyl, aminoalkanoyl, and mono- and disubstituted
aminocarbonyl and mono- and disubstituted aminoalkanoyl

20 radicals wherein the substituents are selected from
alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
heteroaryl, heteroaralkyl, heterocycloalkyl,
heterocycloalkyalkyl radicals, or where said
aminoalkanoyl radical is disubstituted, said substituents

25 along with the nitrogen atom to which they are attached
form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R^3 or
R and R' together with the nitrogen to which they are

30 attached represent heterocycloalkyl and heteroaryl
radical;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$,
$-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$,

35 $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl,

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alkenyl, alkynyl and cycloalkyl radicals, and amino acid
side chains selected from asparagine, S-methyl cysteine
and the sulfoxide (SO) and sulfone (SO$_2$) derivatives
thereof, isoleucine, allo-isoleucine, alanine, leucine,
5   tert-leucine, phenylalanine, ornithine, histidine,
norleucine, glutamine, threonine, allo-threonine, serine,
aspartic acid, beta-cyano alanine and valine side
chains;

10   R^1' and R^1" independently represent hydrogen and radicals
as defined for R^1, or one of R^1' and R^1", together with
R^1 and the carbon atoms to which R^1, R^1' and R^1" are
attached, represent a cycloalkyl radical;

15   R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl
and aralkyl radicals, which radicals are optionally
substituted with a group selected from alkyl and halogen
radials, -NO$_2$, -C≡N, CF$_3$, -OR^9 and -SR^9, wherein R^9
represents hydrogen and alkyl radicals;
20
     R^3 represents alkyl, haloalkyl, alkenyl, alkynyl,
hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
heterocycloalkyl, heteroaryl, heterocycloalkylalkyl,
aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and
25   disubstituted aminoalkyl radicals, wherein said
substituents are selected from alkyl, aryl, aralkyl,
cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl,
heterocycloalkyl, and heterocycloalkylalkyl radicals, or
in the case of a disubstituted aminoalkyl radical, said
30   substituents along with the nitrogen atom to which they
are attached, form a heterocycloalkyl or a heteroaryl
radical; and

     R^4 represents radicals as defined by R^3.
35
          A more preferred family of compounds within
.Formula IV consists of compounds wherein

17

R represents an arylalkanoyl, heteroaroyl,
aryloxyalkanoyl, aryloxycarbonyl, alkanoyl,
aminocarbonyl, mono-substituted aminoalkanoyl, or
5   disubstituted aminoalkanoyl, or mono-or
dialkylaminocarbonyl radical;

R' represents hydrogen and radicals as defined for R^3 or
R and R' together with the nitrogen to which they are
10 attached represent a heterocycloalkyl or heteroaryl
radical;

R^1, $R^{1'}$ and $R^{1''}$ independently represent hydrogen and
alkyl radicals having from 1 to about 4 carbon atoms,
15 alkenyl, alkynyl, aralkyl radicals, and radicals
represented by the formula $-CH_2C(O)R''$ or $-C(O)R''$ wherein
R'' represents R^{38}, $-NR^{38}R^{39}$ and OR^{38} wherein R^{38} and R^{39}
independently represent hydrogen and alkyl radicals
having from 1 to about 4 carbon atoms;
20
R^2 represents alkyl, cycloalkylalkyl and aralkyl
radicals, which radicals are optionally substituted with
halogen radicals and radicals represented by the formula
$-OR^9$ and $-SR^9$ wherein R^9 represents hydrogen and alkyl
25 radicals; and

R^3 and R^4 independently represent alkyl, alkenyl,
alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl,
30 heteroaryl and heteroaralkyl radicals.

        Of highest interest are compounds of Formula IV
wherein:

35 R represents an arylalkanoyl, aryloxycarbonyl,
aryloxyalkanoyl, alkanoyl, aminocarbonyl, mono-

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substituted aminoalkanoyl, or disubstituted
aminoalkanoyl, or mono-or dialkylaminocarbonyl radical;

R' represents hydrogen and radicals as defined for R^3 or
5   R and R' together with the nitrogen to which they are
attached represent a heterocycloalkyl or heteroaryl
radical;

R^1, $R^{1'}$ and $R^{1''}$ independently represent hydrogen, methyl,
10 ethyl, benzyl, phenylpropyl and propargyl radicals;

R^2 represents $CH_3SCH_2CH_2-$, iso-butyl, n-butyl, benzyl,
4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl
radicals;
15

R^3 represents alkyl, cyclohexyl, isobutyl, isoamyl and
n-butyl radicals; and

R^4 represents methyl, phenyl and substituted phenyl
20 radicals wherein the substituents are selected from halo,
alkoxy, amino and nitro substituents.

As utilized herein, the term "alkyl", alone or
in combination, means a straight-chain or branched-chain
25 alkyl radical containing from 1 to about 10 carbon atoms,
preferably from 1 to about 8 carbon atoms, more
preferably 1-5 carbon atoms. Examples of such radicals
include methyl, ethyl, n-propyl, isopropyl, n-butyl,
isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl,
30 octyl and the like. The term "alkenyl", alone or in
combination, means a straight-chain or branched-chain
hydrocarbon radial having one or more double bonds and
containing from 2 to about 18 carbon atoms, preferably
from 2 to about 8 carbon atoms, more preferably from 2 to
35 about 5 carbon atoms. Examples of suitable alkenyl
radicals include ethenyl, propenyl, alkyl, 1,4-butadienyl
and the like. The term "alkynyl", alone or in

combination, means a straight-chain or branched chain
hydrocarbon radical having one or more triple bonds and
containing from 2 to about 10 carbon atoms, more
preferably from 2 to about 5 carbon atoms. Examples of

5 alkynyl radicals include ethynyl, propynyl, (propargyl),
butynyl and the like. The term "alkoxy", alone or in
combination, means an alkyl ether radical wherein the
term alkyl is as defined above. Examples of suitable
alkyl ether radicals include methoxy, ethoxy, n-propoxy,

10 isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy
and the like. The term "cycloalkyl", alone or in
combination, means a saturated or partially saturated
monocyclic, bicyclic or tricyclic alkyl radical wherein
each cyclic moiety contains from about 3 to about 8

15 carbon atoms, more preferably from about 3 to about 6
carbon atoms. Examples of such cycloalkyl radicals
include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl
and the like. The term "cycloalkylalkyl" means an alkyl
radical as defined above which is substituted by a

20 cycloalkyl radical as defined above. Examples of such
cycloalkylalkyl radicals include cyclopropylmethyl,
cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-
cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopentylethyl,
2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl,

25 cyclohexylbutyl and the like. The term "aryl", alone or
in combination, means a phenyl or naphthyl radical which
optionally carries one or more substituents selected from
alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano,
haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl,

30 heterocycloalkyl, amido, mono and dialkyl substituted
amino, mono and dialkyl substituted amido and the like,
such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-
butoxy)phenyl, 3-methyl-4-methoxyphenyl, 4-fluorophenyl,
4-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-

35 acetamidophenyl, 4-acetamidophenyl, 2-methyl-3-
acetamidophenyl, 2-methyl-3-aminophenyl, 3-methyl-4-
aminophenyl, 2-amino-3-methylphenyl, 2,4-dimethyl-3-

20

aminophenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl,
1-naphthyl, 2-naphthyl, 3-amino-1-naphthyl, 2-methyl-3-
amino-1-naphthyl, 6-amino-2-naphthyl, 4,6-dimethoxy-2-
naphthyl and the like. The terms "aralkyl" and

5   "aralkoxy", alone or in combination, means an alkyl or
alkoxy radical as defined above in which at least one
hydrogen atom is replaced by an aryl radical as defined
above, such as benzyl, benzyloxy, 2-phenylethyl,
dibenzylmethyl, hydroxyphenylmethyl, methylphenylmethyl,

10 and the like. The term "aralkoxycarbonyl", alone or in
combination, means a radical of the formula aralkyl-O-
C(O)- in which the term "aralkyl" has the significance
given above. Examples of an aralkoxycarbonyl radical are
benzyloxycarbonyl and 4-methoxyphenylmethoxycarbonyl.

15 The term "aryloxy" means a radical of the formula aryl-O-
in which the term aryl has the significance given above.
The term "alkanoyl", alone or in combination, means an
acyl radical derived from an alkanecarboxylic acid,
examples of which include acetyl, propionyl, butyryl,

20 valeryl, 4-methylvaleryl, and the like. The term
"cycloalkylcarbonyl" means an acyl group derived from a
monocyclic or bridged cycloalkanecarboxylic acid such as
cyclopropylcarbonyl, cyclohexylcarbonyl,
adamantylcarbonyl, and the like, or from a benz-fused

25 monocyclic cycloalkanecarboxylic acid which is optionally
substituted by one or more substituents.selected from
alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano,
haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl,
heterocycloalkyl, alkanoylamino, amido, mono and dialkyl

30 substituted amino, mono and dialkyl substituted amido and
the like, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-
acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The term
"aralkanoyl" means an acyl radical derived from an aryl-
substituted alkanecarboxylic acid such as phenylacetyl,

35 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl,
(2-naphthyl)acetyl, 4-chlorohydrocinnamoyl,
4-aminohydrocinnamoyl,4-methoxyhydrocinnamoyl, and the

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like. The term "aroyl" means an acyl radical derived
from an arylcarboxylic acid, aryl having the meaning
given above. Examples of such arylcarboxylic acid
radicals include substituted and unsubstituted benzoic or
5   naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-
carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-
naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-
(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl,
3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-
10   naphthoyl, and the like. The terms "heterocyclyl" and
"heterocycloalkyl," alone or in combination, mean a
saturated or partially unsaturated monocyclic, bicyclic
or tricyclic heterocycle having preferably 3 to 12 ring
members, more preferably 5 to 10 ring members and most
15   preferably 5 to 6 ring members, which contains one or
more heteroatom ring members selected from nitrogen,
oxygen and sulphur, and which is optionally substituted
on one or more carbon atoms by halogen, alkyl, alkoxy,
hydroxy, oxo, aryl, aralkyl and the like, and/or on a
20   secondary nitrogen atom (i.e., -NH-) by hydroxy, alkyl,
aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl and/or
on a tertiary nitrogen atom (i.e., =N-) by oxido.
Heterocycloalkyl and heterocyclyl also includes benz-
fused monocyclic cycloalkyl groups having at least one
25   such heteroatom. Heterocycloalkyl and heterocyclyl in
addition to sulfur and nitrogen also includes sulfones,
sulfoxides and N-oxides of tertiary nitrogen containing
heterocycloalkyl groups. The term "heteroaryl", alone or
in combination, means an aromatic monocyclic, bicyclic,
30   or tricyclic heterocyclyl (heterocycloalkyl) radical as
defined above and is optionally substituted as defined
above with respect to the definitions of aryl and
heterocyclyl (heterocycloalkyl). Examples of such
heterocyclyl (heterocycloalkyl) and heteroaryl groups are
35   pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,
thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-
yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl,

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pyridyl, (e.g., 2-(1-piperidinyl)pyridyl and 2-(4-benzyl
piperazin-1-yl-1-pyridinyl), pyrazinyl, pyrimidinyl,
furyl, tetrahydrofuryl, thienyl, triazolyl, oxazolyl,
thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl,
5   (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl,
etc.), isoquinolinyl (e.g., 1-isoquinolinyl, 3-
isoquinolinyl, etc.), tetrahydroquinolinyl (e.g.,
1,2,3,4-tetrahydro-2-quinolyl, etc.),
1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-
10   tetrahydro-1-oxo-isoquinolinyl, etc.), quinoxalinyl,
ß-carbolinyl, 2-benzofurancarbonyl, 1-,
2-,4- or 5-benzimidazolyl, and the like. The term
"cycloalkylalkoxycarbonyl" means an acyl group derived
from a cycloalkylalkoxycarboxylic acid of the formula
15   cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the
meaning given above. The term "aryloxyalkanoyl" means an
acyl radical of the formula aryl-O-alkanoyl wherein aryl
and alkanoyl have the meaning given above. The term
"heterocycloalkoxycarbonyl" means an acyl group derived
20   from heterocyclyl-O-COOH wherein heterocyclyl is as
defined above. The term "heterocycloalkylalkanoyl" is an
acyl radical derived from a heterocycloalkyl-substituted
alkylcarboxylic acid wherein heterocycloalkyl has the
meaning given above. The term
25   "heterocycloalkylalkoxycarbonyl" means an acyl radical
derived from a heterocycloalkyl-substituted alkyl-O-COOH
wherein heterocycloalkyl has the meaning given above.
The term "heteroaryloxycarbonyl" means an acyl radical
derived from a carboxylic acid represented by heteroaryl-
30   O-COOH wherein heteroaryl has the meaning given above.
The term "aminocarbonyl" alone or in combination, means
an amino-substituted carbonyl (carbamoyl) group wherein
the amino group can be a primary, secondary or tertiary
amino group containing substituents selected from alkyl,
35   aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and
the like. The term "aminoalkanoyl" means an acyl group
derived from an amino-substituted alkylcarboxylic acid

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wherein the amino group can be a primary, secondary or
tertiary amino group containing substituents selected
from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl
radicals and the like. The term "halogen" means
5   fluorine, chlorine, bromine or iodine. The term
"haloalkyl" means an alkyl radical having the meaning as
defined above wherein one or more hydrogens are replaced
with a halogen. Examples of such haloalkyl radicals
include chloromethyl, 1-bromoethyl, fluoromethyl,
10   difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and
the like. The term "leaving group" generally refers to
groups readily displaceable by a nucleophile, such as an
amine, a thiol or an alcohol nucleophile. Such leaving
groups are well known in the art. Examples of such
15   leaving groups include, but are not limited to,
N-hydroxysuccinimide, N-hydroxybenzotriazole, halides,
triflates, tosylates and the like. Preferred leaving
groups are indicated herein where appropriate. The term
"amino acid side chain" means the side chain group,
20   including the stereochemistry of the carbon to which it
is attached, attached to the naturally occurring amino
acid which distinguishes the amino acid from glycine.
For example, the amino acid side chain of alanine is
methyl, of histidine is imidazolylmethyl and
25   phenylalanine is benzyl, and the attachment of such side
chains to the compound of this invention retain the
naturally occurring stereochemistry of the carbon to
which it is attached. The following example illustrates
the definition:

30

$$R_2N \diagdown CO_2H \implies R\underset{R'}{N}(CR^1R^{1''})_t \diagdown \overset{Y}{\underset{R^1}{\overset{\|}{C}}} \diagdown S$$
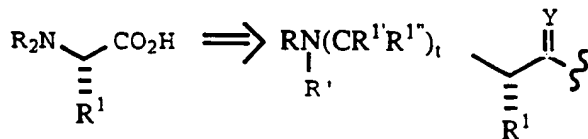
     Procedures for preparing the compounds of
Formula I are set forth below. It should be noted that
35   the general procedure is shown as it relates to

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preparation of compounds having the specified
stereochemistry, for example, wherein the absolute
stereochemistry about the hydroxyl group is designated as
(R). However, such procedures are generally applicable

5   to those compounds of opposite configuration, e.g., where
the stereochemistry about the hydroxyl group is (S). In
addition, the compounds having the (R) stereochemistry
can be utilized to produce those having the (S)
stereochemistry. For example, a compound having the (R)

10 stereochemistry can be inverted to the (S)
stereochemistry using well-known methods.

Preparation of Compounds of Formula I

15   The compounds of the present invention
represented by Formula I above can be prepared utilizing
the following general procedure. This procedure is
schematically shown in the following Schemes I and II:

25

SCHEME I
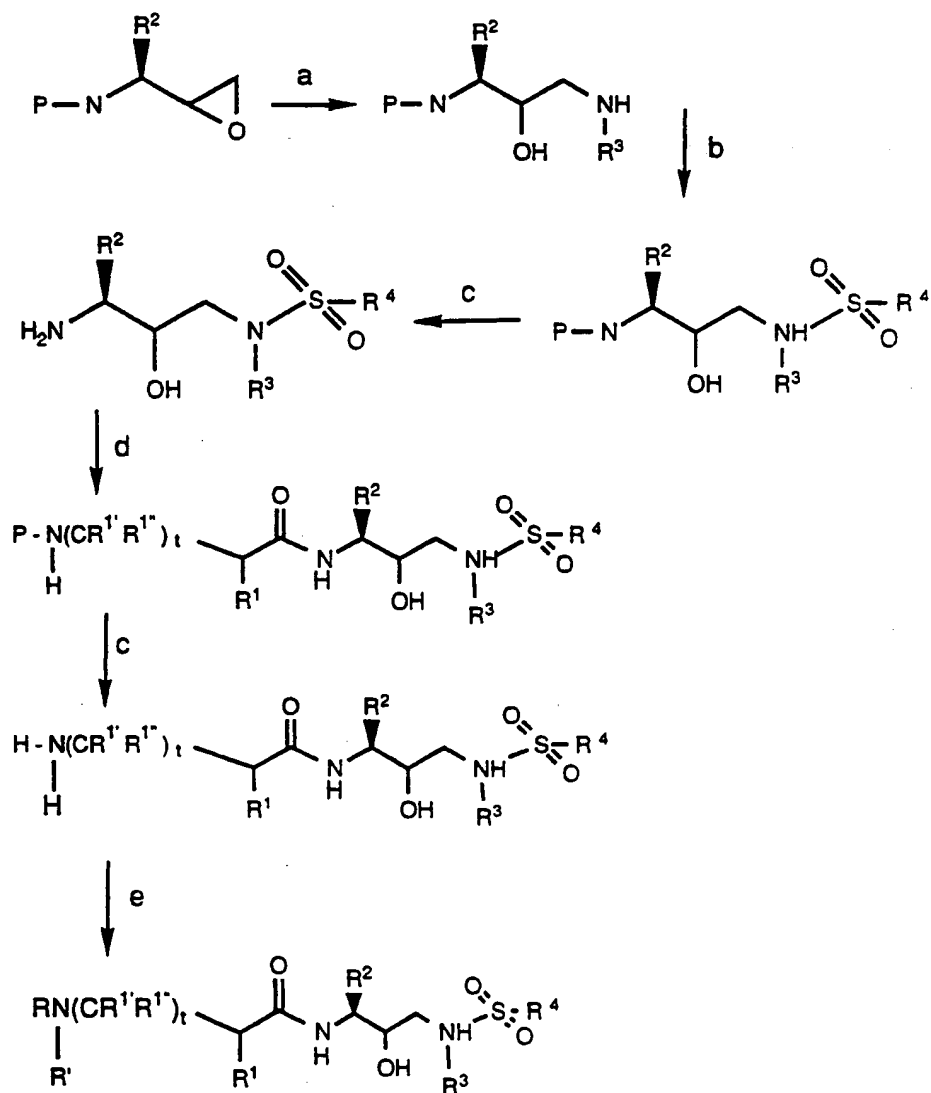
a) amine   b) sulfonyl chloride R^4SO_2Cl (or anhydride) + acid
scavenger   c) deprotection   d) coupling   e) coupling.

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SCHEME II

a) amine b) sulfonyl chloride R⁴SO₂Cl (or anhydride) + acid
5 scavenger c) deprotection d) coupling e) coupling.

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An N-protected chloroketone derivative of an
amino acid having the formula:
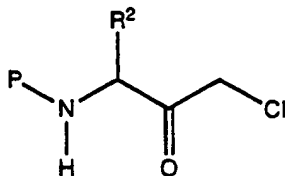
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wherein P represents an amino protecting group, and R^2 is
as defined above, is reduced to the corresponding alcohol
utilizing an appropriate reducing agent. Suitable amino
protecting groups are well known in the art and include
10   carbobenzoxy, t-butoxycarbonyl, and the like. A
preferred amino protecting group is carbobenzoxy. A
preferred N-protected chloroketone is
N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone.
A preferred reducing agent is sodium borohydride. The
15   reduction reaction is conducted at a temperature of from
-10°C to about 25°C, preferably at about 0°C, in a
suitable solvent system such as, for example,
tetrahydrofuran, and the like. The N-protected
chloroketones are commercially available, e.g., such as
20   from Bachem, Inc., Torrance, California. Alternatively,
the chloroketones can be prepared by the procedure set
forth in S. J. Fittkau, _J. Prakt. Chem._, _315_, 1037
(1973), and subsequently N-protected utilizing procedures
which are well known in the art.

25

The halo alcohol can be utilized directly, as
described below, or, preferably, is then reacted,
preferably at room temperature, with a suitable base in a
suitable solvent system to produce an N-protected amino
30   epoxide of the formula:

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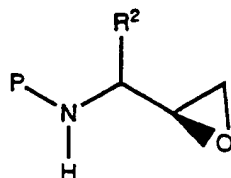
wherein P and R^2 are as defined above. Suitable solvent
systems for preparing the amino epoxide include ethanol,
5   methanol, isopropanol, tetrahydrofuran, dioxane, and the
like including mixtures thereof. Suitable bases for
producing the epoxide from the reduced chloroketone
include potassium hydroxide, sodium hydroxide, potassium
t-butoxide, DBU and the like. A preferred base is
10   potassium hydroxide.

        Alternatively, a protected amino epoxide can be
prepared, such as in co-owned and co-pending PCT Patent
Application Serial No. PCT/US93/04804 which is
15   incorporated herein by reference, starting with an L-
amino acid which is reacted with a suitable amino-
protecting group in a suitable solvent to produce an
amino-protected L-amino acid ester of the formula:
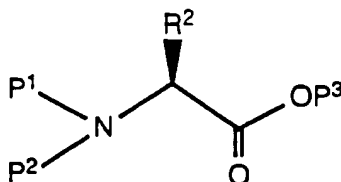
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wherein P^3 represents carboxyl-protecting group, e.g.,
methyl, ethyl, benzyl, tertiary-butyl and the like; R^2 is
as defined above; and P^1 and P^2 independently are selected
25   from amine protecting groups, including but not limited to,
arylalkyl, substituted arylalkyl, cycloalkenylalkyl and
substituted cycloalkenylalkyl, allyl, substituted allyl,
acyl, alkoxycarbonyl, aralkoxycarbonyl and silyl. Examples
of arylalkyl include, but are not limited to benzyl, ortho-
30   methylbenzyl, trityl and benzhydryl, which can be

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optionally substituted with halogen, alkyl of C_1-C_8, alkoxy, hydroxy, nitro, alkylene, amino, alkylamino, acylamino and acyl, or their salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl,
5 naphthalenyl, indanyl, anthracenyl, durenyl, 9-(9-phenylfluorenyl) and phenanthrenyl, cycloalkenylalkyl or substituted cycloalkylenylalkyl radicals containing cycloalkyls of C_6-C_{10}. Suitable acyl groups include carbobenzoxy, t-butoxycarbonyl, iso-butoxycarbonyl,
10 benzoyl, substituted benzoyl, butyryl, acetyl, tri-fluoroacetyl, tri-chloroacetyl, phthaloyl and the like.

Additionally, the P^1 and/or P^2 protecting groups can form a heterocyclic ring with the nitrogen to which they
15 are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted,
20 e.g., nitrophthalimidyl. The term silyl refers to a silicon atom optionally substituted by one or more alkyl, aryl and aralkyl groups.

Suitable silyl protecting groups include, but are
25 not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of the amine functions to provide mono- or bis-
30 disilylamine can provide derivatives of the aminoalcohol, amino acid, amino acid esters and amino acid amide. In the case of amino acids, amino acid esters and amino acid amides, reduction of the carbonyl function provides the required mono- or bis-silyl aminoalcohol. Silylation of the
35 aminoalcohol can lead to the N,N,O-tri-silyl derivative. Removal of the silyl function from the silyl ether function is readily accomplished by treatment with, for example, a

30

metal hydroxide or ammonium flouride reagent, either as a
discrete reaction step or in situ during the preparation of
the amino aldehyde reagent. Suitable silylating agents are,
for example, trimethylsilyl chloride, tert-buty-
5   dimethylsilyl chloride, phenyldimethylsilyl chlorie,
diphenylmethylsilyl chloride or their combination products
with imidazole or DMF. Methods for silylation of amines and
removal of silyl protecting groups are well known to those
skilled in the art. Methods of preparation of these amine
10   derivatives from corresponding amino acids, amino acid
amides or amino acid esters are also well known to those
skilled in the art of organic chemistry including amino
acid/amino acid ester or aminoalcohol chemistry.

15   Preferably P^1 and P^2 are independently selected
from aralkyl and substituted aralkyl. More preferably,
each of P^1 and P^2 is benzyl. As illustrated in the
Examples below, P, P^1 and P^2 may serve as a nitrogen
protecting group which is later removed in the
20   preparation of compounds of this invention or may form a
part of the final inhibitor structure. For example,
benzoyl, benzyloxycarbonyl, t-butoxycarbonyl,
pyridylmethoxycarbonyl, tetrahydrofuryloxycarbonyl,
pyridylcarbonyl and the like can used to both protect a
25   nitrogen from undergoing an undesired reaction and also
be part of the structure of an active enzyme inhibitor.

         The amino-protected L-amino acid ester is then
reduced, to the corresponding alcohol. For example, the
30   amino-protected L-amino acid ester can be reduced with
diisobutylaluminum hydride at -78° C in a suitable
solvent such as toluene. Preferred reducing agents
include lithium aluminium hydride, lithium borohydride,
sodium borohydride, borane, lithium tri-ter-
35   butoxyaluminum hydride, borane/THF complex. Most
preferably, the reducing agent is diisobutylaluminum
hydride (DiBAL-H) in toluene. The resulting alcohol is

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then converted, for example, by way of a Swern oxidation, to the corresponding aldehyde of the formula:
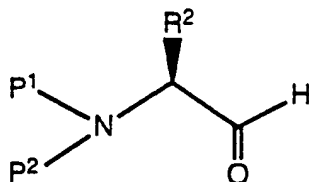
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wherein P^1, P^2 and R^2 are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled (-75 to -68° C) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred
10   for 35 minutes.

        Acceptable oxidizing reagents include, for example, sulfur trioxide-pyridine complex and DMSO, oxalyl chloride and DMSO, acetyl chloride or anhydride
15   and DMSO, trifluoroacetyl chloride or anhydride and DMSO, methanesulfonyl chloride and DMSO or tetrahydro thiaphene-S-oxide, toluenesulfonyl bromide and DMSO, trifluoromethanesulfonyl anhydride (triflic anhydride) and DMSO, phosphorus pentachloride and DMSO,
20   dimethylphosphoryl chloride and DMSO and isobutyl chloroformate and DMSO. The oxidation conditions reported by Reetz et al [Angew Chem., 99, p. 1186, (1987)], Angew Chem. Int. Ed. Engl., 26, p. 1141, 1987) employed oxalyl chloride and DMSO at -78°C.
25

        The preferred oxidation method described in this invention is sulfur trioxide pyridine complex, triethylamine and DMSO at room temperature. This system provides excellent yields of the desired chiral
30   protected amino aldehyde usable without the need for purification i.e., the need to purify kilograms of intermediates by chromatography is eliminated and large scale operations are made less hazardous. Reaction at room temperature also eliminated the need

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for the use of low temperature reactor which makes the
process more suitable for commercial production.

      The reaction may be carried out under and
5   inert atmosphere such as nitrogen or argon, or normal
    or dry air, under atmospheric pressure or in a sealed
    reaction vessel under positive pressure. Preferred is
    a nitrogen atmosphere. Alternative amine bases
    include, for example, tri-butyl amine, tri-isopropyl
10 amine, N-methylpiperidine, N-methyl morpholine,
    azabicyclononane, diisopropylethylamine, 2,2,6,6-
    tetramethylpiperidine, N,N-dimethylaminopyridine, or
    mixtures of these bases. Triethylamine is a preferred
    base. Alternatives to pure DMSO as solvent include
15 mixtures of DMSO with non-protic or halogenated
    solvents such as tetrahydrofuran, ethyl acetate,
    toluene, xylene, dichloromethane, ethylene dichloride
    and the like. Dipolar aprotic co-solvents include
    acetonitrile, dimethylformamide, dimethylacetamide,
20 acetamide, tetramethyl urea and its cyclic analog,
    N-methylpyrrolidone, sulfolane and the like. Rather
    than N,N-dibenzylphenylalaninol as the aldehyde
    precursor, the phenylalaninol derivatives discussed
    above can be used to provide the corresponding
25 N-monosubstituted [either P^1 or P^2 = H] or N,N-
    disubstituted aldehyde.

      In addition, hydride reduction of an amide
    or ester derivative of the corresponding alkyl, benzyl
30 or cycloalkenyl nitrogen protected phenylalanine,
    substituted phenylalanine or cycloalkyl analog of
    phenyalanine derivative can be carried out to provide
    the aldehydes. Hydride transfer is an additional
    method of aldehyde synthesis under conditions where
35 aldehyde condensations are avoided, cf, Oppenauer
    Oxidation.

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The aldehydes of this process can also be prepared by methods of reducing protected phenylalanine and phenylalanine analogs or their amide or ester derivatives by, e.g., sodium amalgam with HCl in ethanol or lithium or

5   sodium or potassium or calcium in ammonia. The reaction temperature may be from about -20°C to about 45°C, and preferably from abut 5°C to about 25°C. Two additional methods of obtaining the nitrogen protected aldehyde include oxidation of the corresponding alcohol with bleach in the

10 presence of a catalytic amount of 2,2,6,6-tetramethyl-1-pyridyloxy free radical. In a second method, oxidation of the alcohol to the aldehyde is accomplished by a catalytic amount of tetrapropylammonium perruthenate in the presence of N-methylmorpholine-N-oxide.

15

Alternatively, an acid chloride derivative of a protected phenylalanine or phenylalanine derivative as disclosed above can be reduced with hydrogen and a catalyst such as Pd on barium carbonate or barium sulphate, with or

20 without an additional catalyst moderating agent such as sulfur or a thiol (Rosenmund Reduction).

The aldehyde resulting from the Swern oxidation is then reacted with a halomethyllithium reagent, which

25 reagent is generated $\underline{in}$ $\underline{situ}$ by reacting an alkyllithium or arylithium compound with a dihalomethane represented by the formula $X^1CH_2X^2$ wherein X^1 and X^2 independently represent I, Br or Cl. For example, a solution of the aldehyde and chloroiodomethane in THF is cooled to -78° C

30 and a solution of n-butyllithium in hexane is added. The resulting product is a mixture of diastereomers of the corresponding amino-protected epoxides of the formulas:

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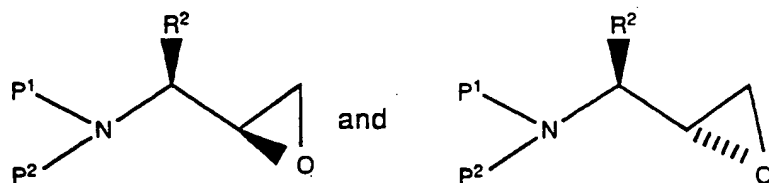
The diastereomers can be separated e.g., by chromatography, or, alternatively, once reacted in subsequent steps the diastereomeric products can be
5   separated. For compounds having the (S) stereochemistry, a D-amino acid can be utilized in place of the L-amino acid.

        The addition of chloromethyllithium or
10 bromomethyllithium to a chiral amino aldehyde is highly diastereoselective. Preferably, the chloromethyllithium or bromomethyllithium is generated in-situ from the reaction of the dihalomethane and n-butyllithium. Acceptable methyleneating halomethanes include chloroiodomethane,
15 bromochloromethane, dibromomethane, diiodomethane, bromofluoromethane and the like. The sulfonate ester of the addition product of, for example, hydrogen bromide to formaldehyde is also a methyleneating agent. Tetrahydrofuran is the preferred solvent, however
20 alternative solvents such as toluene, dimethoxyethane, ethylene dichloride, methylene chloride can be used as pure solvents or as a mixture. Dipolar aprotic solvents such as acetonitrile, DMF, N-methylpyrrolidone are useful as solvents or as part of a solvent mixture. The reaction can
25 be carried out under an inert atmosphere such as nitrogen or argon. For n-butyl lithium can be substituted other organometalic reagents reagents such as methyllithium, tert-butyl lithium, sec-butyl lithium, phenyllithium, phenyl sodium and the like. The reaction can be carried out at
30 temperatures of between about -80°C to 0°C but preferably between about -80°C to -20°C. The most preferred reaction temperatures are between -40°C to -15°C. Reagents can be added singly but multiple additions are preferred in certain conditions. The preferred pressure of the reaction is
35 atmospheric however a positive pressure is valuable under certain conditions such as a high humidity environment.

35

Alternative methods of conversion to the epoxides
of this invention include substitution of other charged
methylenation precurser species followed by their treatment
with base to form the analogous anion. Examples of these
5   species include trimethylsulfoxonium tosylate or triflate,
tetramethylammonium halide; methyldiphenylsulfoxonium halide
wherein halide is chloride, bromide or iodide.

The conversion of the aldehydes of this invention
10   into their epoxide derivative can also be carried out in
multiple steps. For example, the addition of the anion of
thioanisole prepared from, for example, a butyl or aryl
lithium reagent, to the protected aminoaldehyde, oxidation
of the resulting protected aminosulfide alcohol with well
15   known oxidizing agents such as hydrogen peroxide, tert-butyl
hypochlorite, bleach or sodium periodate to give a
sulfoxide. Alkylation of the sulfoxide with, for example,
methyl iodide or bromide, methyl tosylate, methyl mesylate,
methyl triflate, ethyl bromide, isopropyl bromide, benzyl
20   chloride or the like, in the presence of an organic or
inorganic base Alternatively, the protected aminosulfide
alcohol can be alkylated with, for example, the alkylating
agents above, to provide a sulfonium salts that are
subsequently converted into the subject epoxides with tert-
25   amine or mineral bases.

The desired epoxides formed, using most preferred
conditions, diastereoselectively in ratio amounts of at
least about an 85:15 ratio (S:R). The product can be
30   purified by chromatography to give the diastereomerically
and enantiomerically pure product but it is more
conveniently used directly without purification to prepare
retroviral protease inhibitors. The foregoing process is
applicable to mixtures of optical isomers as well as
35   resolved compounds. If a particular optical isomer is
desired, it can be selected by the choice of starting
material, e.g., L-phenylalanine, D-phenylalanine, L-

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phenylalaninol, D-phenylalaninol, D-hexahydrophenylalaninol
and the like, or resolution can occur at intermediate or
final steps. Chiral auxiliaries such as one or two
equivilants of camphor sulfonic acid, citric acid, camphoric
5   acid, 2-methoxyphenylacetic acid and the like can be used to
form salts, esters or amides of the compounds of this
invention. These compounds or derivatives can be
crystallized or separated chromatographically using either a
chiral or achiral column as is well known to those skilled
10   in the art.

        The amino epoxide is then reacted, in a
suitable solvent system, with an equal amount, or
preferably an excess of, a desired amine of the formula
15   R^3NH_2, wherein R^3 is hydrogen or is as defined above.
The reaction can be conducted over a wide range of
temperatures, e.g., from about 10°C to about 100°C, but
is preferably, but not necessarily, conducted at a
temperature at which the solvent begins to reflux.
20   Suitable solvent systems include protic, non-protic and
dipolar aprotic organic solvents such as, for example,
those wherein the solvent is an alcohol, such as
methanol, ethanol, isopropanol, and the like, ethers such
as tetrahydrofuran, dioxane and the like, and toluene,
25   N,N-dimethylformamide, dimethyl sulfoxide, and mixtures
thereof. A preferred solvent is isopropanol. Exemplary
amines corresponding to the formula R^3NH_2 include benzyl
amine, isobutylamine, n-butyl amine, isopentyl amine,
isoamylamine, cyclohexanemethyl amine, naphthylene methyl
30   amine and the like. The resulting product is a 3-(N-
protected amino)-3-(R^2)-1-(NHR^3)-propan-2-ol derivative
(hereinafter referred to as an amino alcohol) can be
represented by the formulas:

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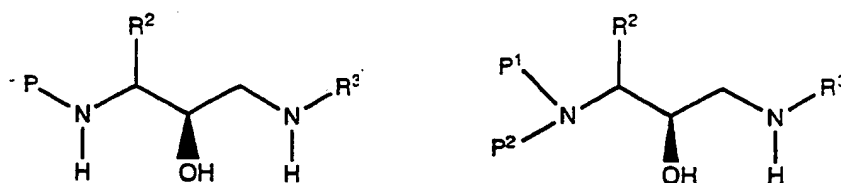
wherein P, P1, P2, R2 and R3 are as described above.
Alternatively, a haloalcohol can be utilized in place of
5   the amino epoxide.

The amino alcohol defined above is then reacted
in a suitable solvent with a sulfonyl chloride (R4SO2Cl)
or sulfonyl anhydride in the presence of an acid
10   scavenger. Suitable solvents in which the reaction can
be conducted include methylene chloride, tetrahydrofuran.
Suitable acid scavengers include triethylamine, pyridine.
Preferred sulfonyl chlorides are methanesulfonyl chloride
and benzenesulfonyl chloride. The resulting sulfonamide
15   derivative can be represented, depending on the epoxide
utilized by the formulas
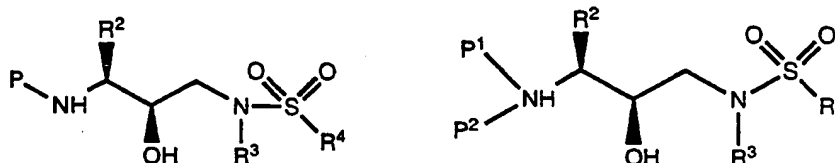
20   wherein P, P1, P2, R2, R3 and R4 are as defined above.
These intermediates are useful for preparing inhibitor
compounds of the present invention and are also active
inhibitors of retroviral proteases.

25   The sulfonyl halides of the formula R4SO2X can
be prepared by the reaction of a suitable Grignard or
alkyl lithium reagent with sulfuryl chloride, or sulfur
dioxide followed by oxidation with a halogen, preferably
chlorine. Also, thiols may be oxidized to sulfonyl
30   chlorides using chlorine in the presence of water under
carefully controlled conditions. Additionally, sulfonic

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acids may be converted to sulfonyl halides using reagents
such as PCl5, and also to anhydrides using suitable
dehydrating reagents. The sulfonic acids may in turn be
prepared using procedures well known in the art. Such

5 sulfonic acids are also commercially available. In place
of the sulfonyl halides, sulfinyl halides (R^4SOX) or
sulfenyl halides (R^4SX) can be utilized to prepare
compounds wherein the $-SO_2-$ moiety is replaced by an -SO-
or -S- moiety, respectively.

10

        Following preparation of the sulfonamide
derivative, the amino protecting group P or P^1 and P^2
amino protecting groups are removed under conditions
which will not affect the remaining portion of the

15 molecule. These methods are well known in the art and
include acid hydrolysis, hydrogenolysis and the like. A
preferred method involves removal of the protecting
group, e.g., removal of a carbobenzoxy group, by
hydrogenolysis utilizing palladium on carbon in a

20 suitable solvent system such as an alcohol, acetic acid,
and the like or mixtures thereof. Where the protecting
group is a t-butoxycarbonyl group, it can be removed
utilizing an inorganic or organic acid, e.g., HCl or
trifluoroacetic acid, in a suitable solvent system, e.g.,

25 dioxane or methylene chloride. The resulting product is
the amine salt derivative. Following neutralization of
the salt, the amine is then reacted with an amino acid or
corresponding derivative thereof represented by the
formula ($PN[CR^{1'}\ R^{1''}]_t\ CH(R^1)COOH$) wherein t, R^1, $R^{1'}$ and

30 $R^{1''}$ are as defined above, to produce the antiviral
compounds of the present invention having the formula:

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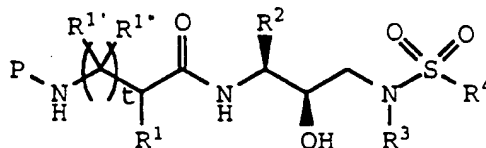
wherein t, P, R^1, R$^{1'}$, R$^{1''}$, R^2, R^3 and R^4 are as defined
above.   Preferred protecting groups in this instance are
a benzyloxycarbonyl group or a t-butoxycarbonyl group.
Where t is O and R^1 is alkyl, alkenyl, alkynyl,
5   cycloalkyl, -CH$_2$SO$_2$NH$_2$, -CH$_2$CO$_2$CH$_3$, -CO$_2$CH$_3$, -CONH$_2$,
-CH$_2$C(O)NHCH$_3$, -C(CH$_3$)$_2$(SH), -C(CH$_3$)$_2$(SCH$_3$),
-C(CH$_3$)$_2$[S(O)CH$_3$], -C(CH$_3$)$_2$[S(O$_2$)CH$_3$], or an amino acid
side chain, such materials are well known and many are
commercially available from Sigma-Aldrich.
10

Where the amine is reacted with a derivative of
an amino acid, e.g., when t=1, so that the amino acid is
a ß-amino acid, such ß-amino acids can be prepared
according to the procedure set forth in a co-owned,
15   copending patent application, U.S. Serial No. 07/853,561
or the following procedures.

Various methods have been proposed for the
preparation of chiral β-amino acids. See, for example,
20   Chemistry and Biochemistry of Amino Acids, Vol. 4,
Chapter 5, pp. 250-57, B. Weinstein, Ed., Dekker, N.Y.
(1975). Furukawa et al, Chem. Pharm. Bull., 25, 1319
(1977), disclose asymmetric synthesis of β-amino acids by
addition of chiral amines to carbon-carbon double bonds
25   having nitrile or ester groups in the α-position.
However, optical purities of the β-amino acids thus
produced range from 2 to 19%. Furukawa et al also report
that optically active β-amino acids have been produced
with optical purities ranging from 2 to 28% by reacting
30   chiral Schiff bases with Reformsky reagent. Terentev et
al, Dohl. Ahad. Nauh SSR, 163,674 (1965) disclose
synthesis of β-aminobutyric acids involving addition of
chiral amines to crotonic acid with optical purities
ranging from 7-9%.
35

Brown et al, Tetrahedron Lett., Vol. 28, No.
19, pp 2179-2182 (1987), disclose a method of preparing

40

optically active disubstituted β-amino acids which
involves asymmetric catalytic hydrogenation of N-
substituted α-(aminoalkyl) acrylates. In order to verify
the stereochemistry of the product, Curtius rearrangement
5   was effected on the monomethyl ester of optically
enriched RR-anti-2,3-dimethyl-succinic acid and trapping
of the incipient isocyanate derivative with tertiary
alcohol, namely, t-butyl alcohol, to give the
corresponding R-enriched β-amino acid. Ninomita et al,
10 Tetrahedron Lett., Vol. 30, 2152-2157 (1975) studied the
Curtius rearrangement utilizing benzoic acid,
diphenylphosphoryl azide and triethylamine followed by
treatment with various alcohols and found that t-butyl
alcohol gives yields superior to benzyl alcohol, ethanol
15 and phenol.

        Utilization of a primary or secondary alcohol
to trap an isocyanate derivative of a chiral mono-
substituted succinate, and, in particular, in a Curtius
20 rearrangement of a chiral mono-substituted succinate, to
produce chiral β-amino acids significantly increases the
overall yield. The resulting carbamate-protected β-amino
esters are then saponified to produce the corresponding
carbamate-protected β-amino acids which are then
25 deprotected to produce β-amino acids possessing the same
absolute configuration as naturally-occurring (L)-amino
acids. The overall reaction sequence can be shown as
follow:

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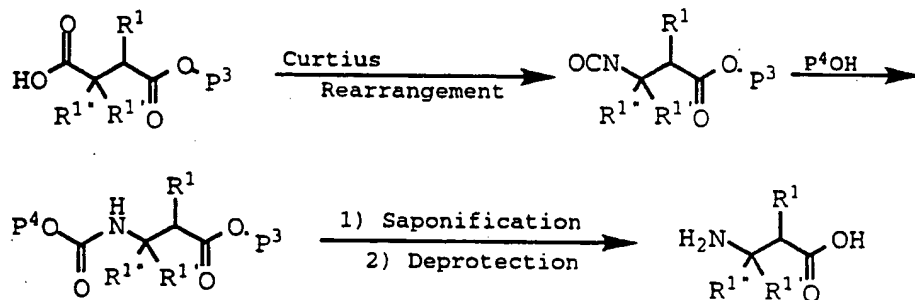
wherein R^1, $R^{1'}$, R^{1*}, and P^3 are as defined above and P^4OH are preferably represents radicals derived from primary and secondary alcohols.

5   This process can also be used in the asymetric synthesis of β-amino acids represented by the formula:

$$H_2N - \overset{\overset{\displaystyle R^{1'}R^1}{\displaystyle |\ \ \blacktriangledown}}{\underset{\underset{\displaystyle R^{1*}}{\displaystyle |}}{C}} - CH - CO_2H$$
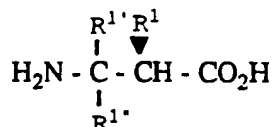
10   wherein R^1, $R^{1'}$ and R^{1*} are as defined above. Such compounds are formed by Curtius rearrangement of 2(R)-substituted succinates represented by the formula

$$HO - \overset{\overset{\displaystyle O}{\displaystyle \|}}{C} - \overset{\overset{\displaystyle R^{1'}R^1}{\displaystyle |\ \ \blacktriangledown}}{\underset{\underset{\displaystyle R^{1*}}{\displaystyle |}}{C}} - CH - CO_2P^3$$
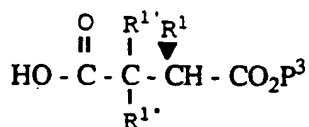
15

wherein R^1, $R^{1'}$, R^{1*} and P^3 are as defined above, to afford the isocyanate derivative:

$$OCN - \overset{\overset{\displaystyle R^{1'}\ R^1}{\displaystyle |\ \ \blacktriangledown}}{\underset{\underset{\displaystyle R^{1*}}{\displaystyle |}}{C}} - CH - CO_2$$
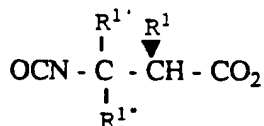
20

Using 2(S)-substituted succinates, 2(S)-substituted β-amino acids can also be prepared stereospecifically.

          Curtius rearrangement involves pyrolysis of
25   acyol azides $(R-\overset{\overset{\displaystyle O}{\displaystyle \|}}{C}-N=N=N)$ to yield isocyanates (R-N=C=O) which can be subsequently hydrolyzed to give amines. See March, Advanced Organic Chemistry, p. 1005, 2nd ed (1977). As a general rule, Curtius rearrangement is a concerted reaction and therefore proceeds with retention
30   of configuration of the starting materials.

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Determination of specific reaction conditions for
effecting Curtius rearrangements of various succinates is
within the skill of one in the art familiar with such
reactions. In the method of the present invention,
5   Curtius rearrangement to afford the desired isocyante is
preferably effected by treating a 2-substituted succinate
with one equivalent of diphenoxyphosphoryl azide
$(PhO)_2PON_3$ and triethylamine to form the acyl azide
followed by heating in an inert solvent, such as in warm
10 toluene, preferably at about 80°C for about three hours,
to afford the isocyante derivative.

        Suitable primary and secondary alcohols include
those represented by the formula P^4OH where P^4
15 representes substituted and unsubstituted alkyl,
cycloalkyl, aralkyl and aryl radicals, as well as
suitable equivalents such as, for example, silyl
radicals. Preferably, the primary and secondary alcohols
are those wherein P^4 represents substituted and
20 unsubstituted, straight chain as well as branched chain,
alkyl radicals having from 1 to about 12 carbon atoms,
substituted and unsubstituted cycloalkyl radicals having
from 4 to about 7 carbon atoms, and substituted and
unsubstituted aryl, alkaryl and aralkyl radicals.
25 Examples of such suitable alcohols include benzyl
alcohol, isopropyl alcohol, 4-methoxybenzyl alcohol, 2-
trimethylsilylethanol, fluorenyl methanol and benzhydrol.
Preferred alcohols are benzyl alcohol and 4-methoxybenzyl
alcohol. Other primary and secondary alcohols suitable
30 for use in the practice of the present invention will be
readily apparent to those skilled in the art.

        The ester derivative is then saponified by any
one of numerous well-known procedures, such as by
35 treatment with aqueous lithium hydroxide/THF
(tetrahydrofuran), preferably for three hours at 0°C.
The resultant product is the corresponding carbamate-

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protected β-amino acids. These are subsequently
deprotected by any one of several well-known procedures,
such as by acid catalyzed hydrolysis or by
hydrogenolysis, to produce the corresponding deprotected
5   β-amino acids. Alternatively, the carbamate-protected β-
amino acid can be coupled to the amine

$$H_2N \overset{R^2}{\diagup} \overset{}{\diagdown} \overset{}{\underset{OH}{\diagup}} \overset{}{\diagdown} \overset{}{\underset{R^3}{N}} \overset{O \diagdown \diagup O}{\underset{}{S}} R^4$$
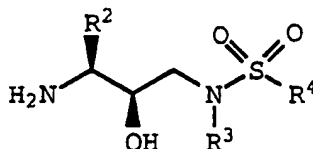
followed by deprotection and incorporation of R and R'.
10

        The N-protecting group can be subsequently
removed, if desired, utilizing the procedures described
above, and then reacted with a carboxylate represented by

the formula $R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}L$, wherein R is as defined above and
15 L is an appropriate leaving group such as a halide.
Preferably, where R^1 is a side chain of a naturally
occurring α-amino acid, R is a 2-quinoline carbonyl group
derived from N-hydroxysuccinimide-2-quinoline
carboxylate. i.e., L is hydroxy succinimide. A solution
20 of the free amine (or amine acetate salt) and about 1.0
equivalent of the carboxylate are mixed in an appropriate
solvent system and optionally treated with up to five
equivalents of a base such as, for example, N-
methylmorpholine, at about room temperature. Appropriate
25 solvent systems include tetrahydrofuran, methylene
chloride or N,N-dimethyl formamide, and the like,
including mixtures thereof.

        Alternatively, the protected amino alcohol from
30 the epoxide opening can be further protected at the newly
introduced amino group with a protecting group P' which is
not removed when the first protecting P is removed. One
skilled in the art can choose appropriate combinations of P

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and P'. One suitable choice is when P is Cbz and P' is Boc.
The resulting compound represented by the formula:

$$P-\underset{\underset{H}{|}}{N}-\underset{\underset{R^2}{|}}{CH}-CH(OH)-CH_2-\underset{\underset{R^3}{|}}{N}-P'$$
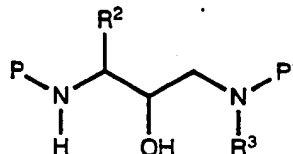
5

can be carried through the remainder of the synthesis to
provide a compound of the formula:

$$R-N(CR^{1'}R^{1''})-\underset{\underset{R'}{|}}{CH}-\underset{\underset{R^1}{|}}{CH}-\overset{O}{\overset{||}{C}}-NH-\underset{\underset{OH}{|}}{CH}(R^2)-CH-CH_2-\underset{\underset{R^3}{|}}{N}-P'$$
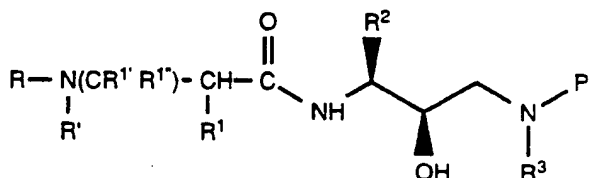
10

and the new protecting group P' is selectively removed,
and following deprotection, the resulting amine reacted to
form the sulfonamide derivative as described above. This
selective deprotection and conversion to the sulfonamide
15   can be accomplished at either the end of the synthesis or
at any appropriate intermediate step if desired.

        The thiocarbonyl compounds of this invention
are really prepared by methods well known to those
20   skilled in the art, for example, by treatment of a
carbonyl compound with Lawesson's reagent (2,4-bis(4-
methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-
disulfide) which is an article of commerce. Phosphorus
pentasulfide may also be used or one can treat an amine
25   of this invention with a pre-formed thiocarbonyl reagent
such as thiocarbonylchlorid in the presence of base.

        In place of the sulfonyl halides, sulfinyl
halides (RSOCl) and sulfenyl halides (RSCl) can be
30   utilized to prepare compounds wherein the $-SO_2-$ moiey is
replaced by $-SO-$ or $-S-$, respectively.

45

It is contemplated that for preparing compounds
of the Formulas having R^6, the compounds can be prepared
following the procedure set forth above and, prior to
5   coupling the sulfonamide derivative or analog thereof,
e.g. coupling to the amino acid $PNH(CH_2)_tCH(R^1)COOH$,
carried through a procedure referred to in the art as
reductive amination. Thus, a sodium cyanoborohydride and
an appropriate aldehyde or ketone can be reacted with the
10   sulfonamide derivative compound or appropriate analog at
room temperature in order to reductively aminate any of
the compounds of Formulas I-IV. It is also contemplated
that where R^3 of the amino alcohol intermediate is
hydrogen, the inhibitor compounds of the present
15   invention wherein R^3 is alkyl, or other substituents
wherein the α-C contains at least one hydrogen, can be
prepared through reductive amination of the final product
of the reaction between the amino alcohol and the amine
or at any other stage of the synthesis for preparing the
20   inhibitor compounds.

Contemplated equivalents of the general
formulas set forth above for the antiviral compounds and
derivatives as well as the intermediates are compounds
25   otherwise corresponding thereto and having the same
general properties, such as tautomers thereof as well as
compounds, wherein one or more of the various R groups
are simple variations of the substituents as defined
therein, e.g., wherein R is a higher alkyl group than
30   that indicated. In addition, where a substituent is
designated as, or can be, a hydrogen, the exact chemical
nature of a substituent which is other than hydrogen at
that position, e.g., a hydrocarbyl radical or a halogen,
hydroxy, amino and the like functional group, is not
35   critical so long as it does not adversely affect the
overall activity and/or synthesis procedure.

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The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be
5   applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications
10   known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise
15   conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

20   Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative,
25   and not limitative of the remainder of the disclosure in any way whatsoever.

All reagents were used as received without purification. All proton and carbon NMR spectra were
30   obtained on either a Varian VXR-300 or VXR-400 nuclear magnetic resonance spectrometer.

The following Examples 1 through 9 illustrate preparation of intermediates. These intermediates are
35   useful in preparing the inhibitor compounds of the

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present invention as illustrated in Examples 10-16. In
addition, the intermediates of Examples 2-6 are also
retroviral protease inhibitors and inhibit, in
particular, HIV protease.

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<u>Example 1A</u>
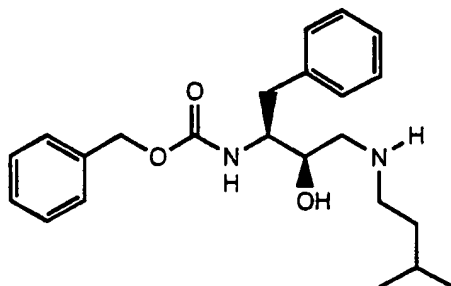
10   <u>Preparation of N[3(S)-benzyloxycarbonylamino-2(R)-</u>
     <u>hydroxy-4-phenylbutyl]-N-isoamylamine</u>

<u>Part A</u>:

         To a solution of 75.0g (0.226 mol) of
15   N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone
     in a mixture of 807 mL of methanol and 807 mL of
     tetrahydrofuran at -2°C, was added 13.17g (0.348 mol,
     1.54 equiv.) of solid sodium borohydride over one hundred
     minutes. The solvents were removed under reduced
20   pressure at 40°C and the residue dissolved in ethyl
     acetate (approx. 1L). The solution was washed
     sequentially with 1M potassium hydrogen sulfate,
     saturated sodium bicarbonate and then saturated sodium
     chloride solutions. After drying over anhydrous
25   magnesium sulfate and filtering, the solution was removed
     under reduced pressure. To the resulting oil was added
     hexane (approx. 1L) and the mixture warmed to 60°C with
     swirling. After cooling to room temperature, the solids
     were collected and washed with 2L of hexane. The
30   resulting solid was recrystallized from hot ethyl acetate
     and hexane to afford 32.3g (43% yield) of

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N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-
butanol, mp 150-151°C and M+Li+ = 340.

Part B:

5   To a solution of 6.52g (0.116 mol, 1.2 equiv.)
of potassium hydroxide in 968 mL of absolute ethanol at
room temperature, was added 32.3g (0.097 mol) of N-CBZ-
3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After
stirring for fifteen minutes, the solvent was removed
10   under reduced pressure and the solids dissolved in
methylene chloride. After washing with water, drying
over magnesium sulfate, filtering and stripping, one
obtains 27.9g of a white solid. Recrystallization from
hot ethyl acetate and hexane afforded 22.3g (77% yield)
15   of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-
phenylbutane, mp 102-103°C and MH+ 298.

Part C:

          A solution of N-benzyloxycarbonyl 3(S)-amino-
20   1,2-(S)-epoxy-4-phenylbutane (1.00g, 3.36 mmol) and
isoamylamine (4.90g, 67.2 mmol, 20 equiv.) in 10 mL of
isopropyl alcohol was heated to reflux for 1.5 hours.
The solution was cooled to room temperature, concentrated
in vacuo and then poured into 100 mL of stirring hexane
25   whereupon the product crystallized from solution. The
product was isolated by filtration and air dried to give
1.18g, 95% of N=[[3(S)-phenylmethylcarbamoyl)amino-2(R)-
hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine mp 108.0-
109.5°C, MH+ m/z = 371.

30

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Example 1B
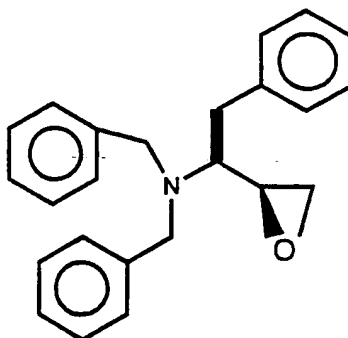
5   Preparation of N,N-dibenzyl-3(S)-amino-1,2-(S)-epoxy-4-
phenylbutane

Step A:

A solution of L-phenylalanine (50.0 g, 0.302 mol),
10   sodium hydroxide (24.2 g, 0.605 mol) and potassium
carbonate (83.6 g, 0.605 mol) in water (500 ml) was
heated to 97°C. Benzyl bromide (108.5 ml, 0.912 mol) was
then slowly added (addition time ~25 min). The mixture
was then stirred at 97°C for 30 minutes. The solution
15   was cooled to room temperature and extracted with toluene
(2 x 250 ml). The combined organic layers were then
washed with water, brine, dried over magnesium sulfate,
filtered and concentrated to give an oil product. The
crude product was then used in the next step without
20   purification.

Step B:

The crude benzylated product of the above step was
dissolved in toluene (750 ml) and cooled to -55°C. A 1.5
25   M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol)
was then added at a rate to maintain the temperature
between -55° to -50°C (addition time - 1 hour). The
mixture was stirred for 20 minutes at -55°C. The
reaction was quenched at -55°C by the slow addition of

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methanol (37 ml). The cold solution was then poured into
cold (5°C) 1.5 N HCl solution (1.8 L). The precipitated
solid (approx. 138 g) was filtered off and washed with
toluene. The solid material was suspended in a mixture

5   of toluene (400 ml) and water (100 ml). The mixture was
cooled to 5°C, treated with 2.5 N NaOH (186 ml) and then
stirred at room temperature until the solid was
dissolved. The toluene layer was separated from the
aqueous phase and washed with water and brine, dried over

10 magnesium sulfate, filtered and concentrated to a volume
of 75 ml (89 g). Ethyl acetate (25 ml) and hexane (25
ml) were then added to the residue upon which the alcohol
product began to crystallize. After 30 min., an
additional 50 ml hexane was added to promote further

15 crystallization. The solid was filtered off and washed
with 50 ml hexane to give approximately 35 g of material.
A second crop of material could be isolated by
refiltering the mother liquor. The solids were combined
and recrystallized from ethyl acetate (20 ml) and hexane

20 (30 ml) to give, in 2 crops, approximately 40 g (40% from
L-phenylalanine) of analytically pure alcohol product.
The mother liquors were combined and concentrated (34 g).
The residue was treated with ethyl acetate and hexane
which provided an additional 7 g (~7% yield) of slightly

25 impure solid product. Further optimization in the
recovery from the mother liquor is probable.

Alternatively, the alcohol was prepared from L-
phenylalaninol. L-phenylalaninol (176.6 g, 1.168 mol)

30 was added to a stirred solution of potassium carbonate
(484.6 g, 3.506 mol) in 710 mL of water. The mixture
was heated to 65°C under a nitrogen atmosphere. A
solution of benzyl bromide (400 g, 2.339 mol) in 3A
ethanol (305 mL) was added at a rate that maintained

35 the temperature between 60-68°C. The biphasic
solution was stirred at 65°C for 55 min and then
allowed to cool to 10°C with vigorous stirring. The

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oily product solidified into small granules. The
product was diluted with 2.0 L of tap water and
stirred for 5 minutes to dissolve the inorganic by
products. The product was isolated by filtration
5   under reduced pressure and washed with water until the
pH is 7. The crude product obtained was air dried
overnite to give a semi-dry solid (407 g) which was
recrystallized from 1.1 L of ethyl acetate/heptane
(1:10 by volume). The product was isolated by
10   filtration (at -8°C), washed with 1.6 L of cold
(-10°C) ethyl acetate/heptane (1:10 by volume) and
air-dried to give 339 g (88% yield) of ßS-2-
[Bis(phenylmethyl)amino]benzene-propanol, mp 71.5-
73.0°C. More product can be obtained from the mother
15   liquor if necessary. The other analytical
characterization was identical to compound prepared as
described above.

Step C:

20   A solution of oxalyl chloride (8.4 ml, 0.096 mol) in
dichloromethane (240 ml) was cooled to -74°C. A solution
of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml)
was then slowly added at a rate to maintain the
temperature at -74°C (addition time ~1.25 hr). The
25   mixture was stirred for 5 min. followed by addition of a
solution of the alcohol (0.074 mol) in 100 ml of
dichloromethane (addition time -20 min., temp. -75°C to
-68°C). The solution was stirred at -78°C for 35
minutes. Triethylamine (41.2 ml, 0.295 mol) was then
30   added over 10 min. (temp. -78° to -68°C) upon which the
ammonium salt precipitated. The cold mixture was stirred
for 30 min. and then water (225 ml) was added. The
dichloromethane layer was separated from the aqueous
phase and washed with water, brine, dried over magnesium
35   sulfate, filtered and concentrated. The residue was
diluted with ethyl acetate and hexane and then filtered
to further remove the ammonium salt. The filtrate was

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concentrated to give the desired aldehyde product. The
aldehyde was carried on to the next step without
purification.

5   Temperatures higher than -70°C have been reported in
the literature for the Swern oxidation. Other Swern
modifications and alternatives to the Swern oxidations
are also possible.

10   Alternatively, the aldehyde was prepared as follows.
(200 g, 0.604 mol) was dissolved in triethylamine (300
mL, 2.15 mol). The mixture was cooled to 12°C and a
solution of sulfur trioxide/pyridine complex (380 g, 2.39
mol) in DMSO (1.6 L) was added at a rate to maintain the
15 temperature between 8-17°C (addition time - 1.0 h). The
solution was stirred at ambient temperature under a
nitrogen atmosphere for 1.5 hour at which time the
reaction was complete by TLC analysis (33% ethyl
acetate/hexane, silica gel). The reaction mixture was
20 cooled with ice water and quenched with 1.6 L of cold
water (10-15°C) over 45 minutes. The resultant solution
was extracted with ethyl acetate (2.0 L), washed with 5%
citric acid (2.0 L), and brine (2.2 L), dried over $MgSO_4$
(280 g) and filtered. The solvent was removed on a
25 rotary evaporator at 35-40°C and then dried under vaccuum
to give 198.8 g of αS-[Bis-(phenylmethyl)amino]-
benzenepropanaldehyde as a pale yellow oil (99.9%). The
crude product obtained was pure enough to be used
directly in the next step without purification. The
30 analytical data of the compound were consistent with the
published literature.$[\alpha]_D25$ = -92.9 ° (c 1.87, CH_2Cl_2);
^{1}H NMR (400 MHz, $CDCl_3$) ∂, 2.94 and 3.15 (ABX-System,
2H, J_{AB}= 13.9 Hz, J_{AX}= 7.3 Hz and J_{BX} = 6.2 Hz), 3.56
(t, 1H, 7.1 Hz), 3.69 and 3.82 (AB-System, 4H, J_{AB}= 13.7
35 Hz), 7.25 (m, 15 H) and 9.72 (s, 1H); HRMS calcd for
(M+1) $C_{23}H_{24}NO$ 330.450, found: 330.1836. Anal. Calcd. for
$C_{23}H_{23}ON$: C, 83.86; H, 7.04; N, 4.25. Found: C, 83.64; H,

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7.42; N, 4.19. HPLC on chiral stationary phase:(S,S)
Pirkle—Whelk-O 1 column (250 x 4.6 mm I.D.), mobile
phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5
ml/min, detection with UV detector at 210nm. Retention

5   time of the desired S-isomer: 8.75 min., retention time
of the R-enanatiomer 10.62 min.

Step D:

          A solution of αS-[Bis(phenylmethyl)amino]
10   benzene-propanaldehyde (191.7 g, 0.58 mol) and
chloroiodomethane (56.4 mL, 0.77 mol) in
tetrahydrofuran (1.8 L) was cooled to -30 to -35°C
(colder temperature such as -70°C also worked well but
warmer temperatures are more readily achieved in large
15   scale operations) in a stainless steel reactor under a
nitrogen atmosphere. A solution of n-butyllithium in
hexane (1.6 M, 365 mL, 0.58 mol) was then added at a
rate that maintained the temperature below -25°C.
After addition the mixture was stirred at -30 to -35°C
20   for 10 minutes. More additions of reagents were
carried out in the following manner: (1) additional
chloroiodomethane (17 mL) was added, followed by
n-butyllithium (110 mL) at < -25°C. After addition
the mixture was stirred at -30 to -35°C for 10
25   minutes. This was repeated once. (2) Additional
chloroiodomethane (8.5 mL, 0.11 mol) was added,
followed by n-butyllithium (55 mL, 0.088 mol) at
<-25°C. After addition, the mixture was stirred at
-30 to -35°C for 10 minutes. This was repeated 5
30   times. (3) Additional chloroiodomethane (8.5 mL, 0.11
mol) was added, followed by n-butyllithium (37 mL,
0.059 mol) at <-25°C. After addition, the mixture
was stirred at -30 to -35°C for 10 minutes. This was
repeated once. The external cooling was stopped and
35   the mixture warmed to ambient temp. over 4 to 16 hours
when TLC (silica gel, 20% ethyl acetate/hexane)
indicated that the reaction was completed. The

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reaction mixture was cooled to 10°C and quenched with
1452 g of 16% ammonium chloride solution (prepared by
dissolving 232 g of ammonium chloride in 1220 mL of
water), keeping the temperature below 23°C. The

5   mixture was stirred for 10 minutes and the organic and
aqueous layers were separated. The aqueous phase was
extracted with ethyl acetate (2x 500 mL). The ethyl
acetate layer was combined with the tetrahydrofuran
layer. The combined solution was dried over magnesium

.10   sulfate (220 g), filtered and concentrated on a rotary
evaporator at 65°C. The brown oil residue was dried at
70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of
crude material. (The crude product weight was >100%.
Due to the relative instability of the product on

15   silica gel, the crude product is usually used directly
in the next step without purification). The
diastereomeric ratio of the crude mixture was
determined by proton NMR: (2S)/(2R): 86:14. The minor
and major epoxide diastereomers were characterized in

20   this mixture by tlc analysis (silica gel, 10% ethyl
acetate/hexane), Rf = 0.29 & 0.32, respectively. An
analytical sample of each of the diastereomers was
obtained by purification on silica-gel chromatography
(3% ethyl acetate/hexane) and characterized as

25   follows:

N,N,αS-Tris(phenylmethyl)-2S-oxiranemethanamine

^{1}H NMR (400 MHz, CDCl$_3$) ∂ 2.49 and 2.51 (AB-System,

30   1H, J$_{AB}$ = 2.82), 2.76 and 2.77 (AB-System, 1H, J$_{AB}$ =
4.03), 2.83 (m, 2H), 2.99 & 3.03 (AB-System, 1H, J$_{AB}$ =
10.1 Hz), 3.15 (m, 1H), 3.73 & 3.84 (AB-System, 4H,
J$_{AB}$ = 14.00), 7.21 (m, 15H); ^{13}C NMR (400 MHz,CDCl$_3$)
∂ 139.55, 129.45, 128.42, 128.14, 128.09, 126.84,

35   125.97, 60.32, 54.23, 52.13, 45.99, 33.76; HRMS calcd
for C$_{24}$H$_{26}$NO (M+1) 344.477, found 344.2003.

N,N,αS-Tris(phenylmethyl)-2R-oxiranemethanamine

^{1}H NMR (300 MHz, CDCl$_3$) ∂ 2.20 (m, 1H), 2.59 (m,
5   1H), 2.75 (m, 2H), 2.97 (m, 1H), 3.14 (m, 1H), 3.85
     (AB-System, 4H), 7.25 (m, 15H).HPLC on chiral
     stationary phase: Pirkle-Whelk-O 1 column (250 x 4.6
     mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5,
     v/v), flow-rate: 1.5 ml/min, detection with UV
10   detector at 210nm. Retention time of(8): 9.38 min.,
     retention time of enanatiomer of (4): 13.75 min.

        Alternatively, a solution of the crude
     aldehyde 0.074 mol and chloroiodomethane (7.0 ml,
15   0.096 mol) in tetrahydrofuran (285 ml) was cooled to
     -78°C, under a nitrogen atmosphere. A 1.6 M solution
     of n-butyllithium in hexane (25 ml, 0.040 mol) was
     then added at a rate to maintain the temperature at
     -75°C (addition time - 15 min.). After the first
20   addition, additional chloroiodomethane (1.6 ml, 0.022
     mol) was added again, followed by n-butyllithium (23
     ml, 0.037 mol), keeping the temperature at -75°C. The
     mixture was stirred for 15 min. Each of the reagents,
     chloroiodomethane (0.70 ml, 0.010 mol) and
25   n-butyllithium (5 ml, 0.008 mol) were added 4 more
     times over 45 min. at -75°C. The cooling bath was
     then removed and the solution warmed to 22°C over
     1.5 hr. The mixture was poured into 300 ml of
     saturated aq. ammonium chloride solution. The
30   tetrahydrofuran layer was separated. The aqueous
     phase was extracted with ethyl acetate (1 x 300 ml).
     The combined organic layers were washed with brine,
     dried over magnesium sulfate, filtered and
     concentrated to give a brown oil (27.4 g). The
35   product could be used in the next step without
     purification. The desired diastereomer can be

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purified by recrystallization at a subsequent step.
The product could also be purified by chromatography.

Alternatively, a solution of αS-
5   [Bis(phenylmethyl)amino]benzene-propanaldehyde (178.84
g, 0.54 mol) and bromochloromethane (46 mL, 0.71 mol)
in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C
(colder temperature such as -70°C also worked well but
warmer temperatures are more readily achieved in large
10   scale operations) in a stainless steel reactor under a
nitrogen atmosphere. A solution of n-butyllithium in
hexane (1.6 M, 340 mL, 0.54 mol) was then added at a
rate that maintained the temperature below -25°C.
After addition the mixture was stirred at -30 to -35°C
15   for 10 minutes. More additions of reagents were
carried out in the following manner: (1) additional
bromochloromethane (14 mL) was added, followed by
n-butyllithium (102 mL) at < -25°C. After addition
the mixture was stirred at -30 to -35°C for 10
20   minutes.   This was repeated once.   (2) Additional
bromochloromethane (7 mL, 0.11 mol) was added,
followed by n-butyllithium (51 mL, 0.082 mol) at
<-25°C. After addition the mixture was stirred at -30
to -35°C for 10 minutes. This was repeated 5 times.
25   (3) Additional bromochloromethane (7 mL, 0.11 mol) was
added, followed by n-butyllithium (51 mL, 0.082 mol)
at <-25°C. After addition the mixture was stirred at
-30 to -35°C for 10 minutes. This was repeated once.
The external cooling was stopped and the mixture
30   warmed to ambient temp. over 4 to 16 hours when TLC
(silica gel, 20% ethyl acetate/hexane) indicated that
the reaction was completed. The reaction mixture was
cooled to 10°C and quenched with 1452 g of
16% ammonium chloride solution (prepared by dissolving
35   232 g of ammonium chloride in 1220 mL of water),
keeping the temperature below 23°C. The mixture was
stirred for 10 minutes and the organic and aqueous

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layers were separated. The aqueous phase was
extracted with ethyl acetate (2x 500 mL). The ethyl
acetate layer was combined with the tetrahydrofuran
layer. The combined solution was dried over magnesium
5   sulfate (220 g), filtered and concentrated on a rotary
evaporator at 65°C. The brown oil residue was dried at
70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of
crude material.

10   Example 2
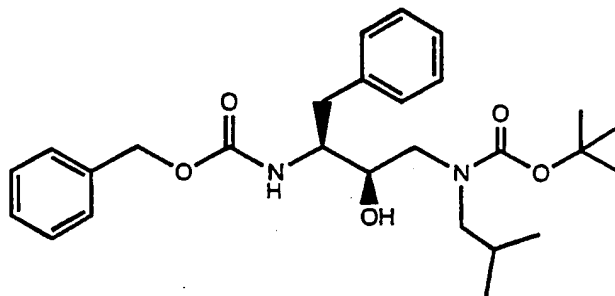
Preparation of N-[[3S-(phenylmethylcarbamoyl)amino]-2R-
15   hydroxy-4-phenyl]-1-[(2-methylpropyl)amino-2-(1,1-
dimethylethoxy)carbonyl]butane

To a solution of 7.51g (20.3 mmol) of N-[[3S-
(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenylbutyl]-
20   N-(2-methylpropyl)]amine in 67 mL of anhydrous
tetrahydrofuran was added 2.25g (22.3 mmol) of
triethylamine. After cooling to 0°C, 4.4g (20.3 mmol) of
di-tert-butyldicarbonate was added and stirring continued
at room temperature for 21 hours. The volatiles were
25   removed in vacuo, ethyl acetate added, then washed with
5% citric acid, saturated sodium bicarbonate, brine,
dried over magnesium sulfate, filtered and concentrated
to afford 9.6g of crude product. Chromatography on
silica gel using 30% ethyl acetate/hexane afforded 8.2g
30   of pure N-[[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-

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4-phenyl]-1-[(2-methylpropyl)amino-2-(1,1-
dimethylethoxyl)carbonyl]butane, mass spectum m/e = 477
(M+Li).

5   Example 3A
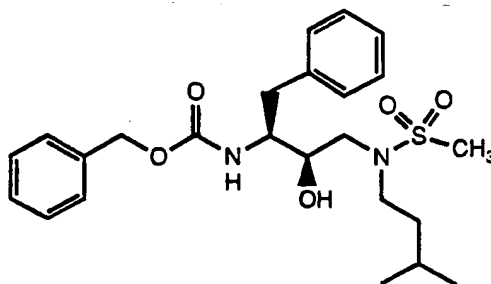
Preparation of phenylmethyl [2R-hydroxy-3-[(3-
10   methylbutyl) (methylsulfonyl)amino]-1S-
(phenylmethyl)propyl]carbamate

        To a solution of N[3(S)-benzyloxycarbonylamino-
2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (2.0 gm, 5.2
15   mmol) and triethylamine (723 uL, 5.5 mmol) in
dichloromethane (20 mL) was added dropwise
methanesulfonyl chloride (400 uL, 5.2 mmol). The
reaction mixture was stirred for 2 hours at room
temperature, then the dichloromethane solution was
20   concentrated to ca. 5 mL and applied to a silica gel
column (100 gm). The column was eluted with chloroform
containing 1% ethanol and 1% methanol. The phenylmethyl
[2R-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-
(phenylmethyl)propyl]carbamate was obtained as a white
25   solid Anal. Calcd for C24H34N2O5S: C, 62.31; H, 7.41; N,
6.06. Found: C, 62.17; H, 7.55; N, 5.97.
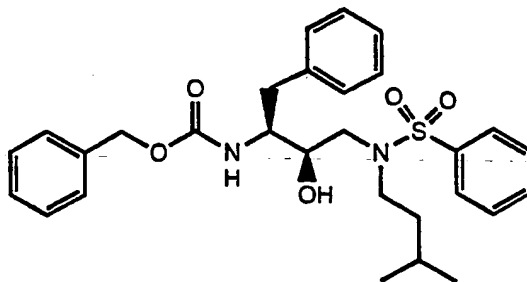
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Example 3B

5   Preparation of phenylmethyl [2R-hydroxy-3-[(3-
     methylbutyl) (phenylsulfonyl)amino]-1S-
     (phenylmethyl)propyl]carbamate

          From the reaction of N[3(S)-
10   benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]
     N-isoamylamine (1.47 gm, 3.8 mmol), triethylamine (528
     uL, 3.8 mmol) and benzenesulfonyl chloride (483 uL, 3.8
     mmol) one obtains   phenylmethyl [2R-hydroxy-3-[(3-
     methylbutyl) (phenylsulfonyl)amino]-1S-
15   (phenylmethyl)propyl]-carbamate. Column chromotography
     on silica gel eluting with chloroform containing 1%
     ethanol afforded the pure product. Anal. Calcd for
     $C_{29}H_{36}N_2O_5S$: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.37;
     H, 6.93; N, 5.26.
20
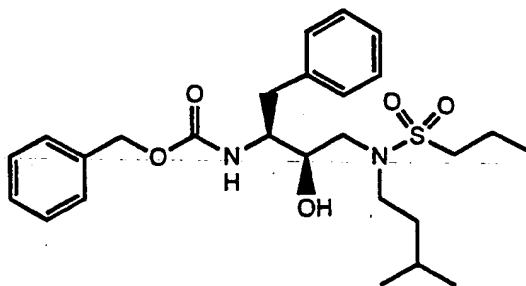
Example 4

5   Preparation of Phenylmethyl [2R-hydroxy-3-[(3-
     methylbutyl) (n-propanesulfonyl)amino]-1S-
     (phenylmethyl)propyl]carbamate

          To a solution of N[3(S)-benzyloxycarbonylamino-
10   2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (192 mg , 0.5
     mmol) and triethylamine (139 uL, 1.0 mmol) in
     dichloromethane (10 mL) was added dropwise trimethylsilyl
     chloride (63 uL, 0.5 mmol). The reaction was allowed to
     stir for 1 hour at room temperature, cooled to 0° C with
15   an ice bath and then n-propanesulfonyl chloride (56 uL,
     0.5 mmol) was added dropwise. The reaction mixture was
     stirred for 1.5 hours at room temperature, then diluted
     with ethyl acetate (50 mL) and washed sequentially with
     1N HCl, water, saturated sodium bicarbonate solution, and
20   saturated sodium chloride solution (25 mL each). The
     organic solution was dried over magnesium sulfate,
     filtered and concentrated to an oil. The oil was stirred
     with methanol (10 mL) for 16 hours, concentrated and the
     residue chromatographed on silica gel (50 gm) eluting
25   with 10% ethyl acetate in hexane (450 mL), then with 1:1
     ethyl acetate / hexane. The phenylmethyl [2R-hydroxy-3-
     [(3-methylbutyl) (n-propanesulfonyl)amino]-1S-
     (phenylmethyl)propyl]carbamate was recrystallized from
     ethyl ether / hexane to afford a white solid Anal. Calcd.
30   for $C_{26}H_{38}N_2O_5S$: C, 63.64; H, 7.81; N, 5.71. Found: C,
     63.09; H, 7.74; N, 5.64.

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Example 5

5
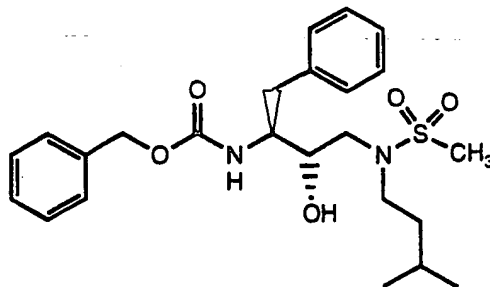
The procedure described in Example 2 was used to prepare
phenylmethyl [2S-hydroxy-3-[(3-methylbutyl)
10   (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate.

To a solution of N[3(S)-benzyloxycarbonylamino-2(S)-
hydroxy-4-phenylbutyl] N-isoamylamine (192 mg, 0.5 mmol)
and triethylamine (139 uL, 0.55 mmol) in dichloromethane
15   (8 mL) was added dropwise methanesulfonyl chloride (39
uL, 0.55 mmol). The reaction mixture was stirred for 16
hours at room temperature, then the dichloromethane
solution was applied to a silica gel column (50 gm). The
column was eluted with dichloromethane containing 2.5%
20   methanol. The phenylmethyl [2S-hydroxy-3-[(3-
methylbutyl) (methylsulfonyl)amino]-1S-
(phenylmethyl)propyl]carbamate was obtained as a white
solid Anal. Calcd. for $C_{24}H_{34}N_2O_5S$ ◊ 0.2 H_2O: C, 61.83;
H, 7.44; N, 6.01. Found: C, 61.62; H, 7.40; N, 5.99.

25

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Example 6

Following the procedures of the previous Examples 1-5, the compounds set forth in Tables 1A and 1B were
5 prepared.

TABLE 1A

10
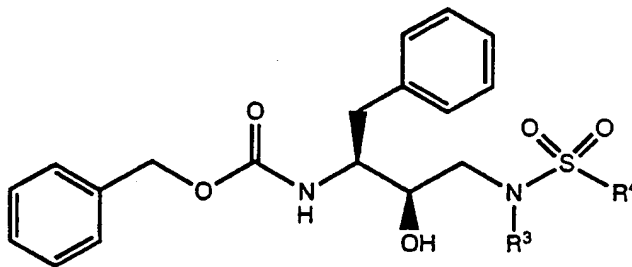
Entry	R^3	R^4
1	isoamyl	p-fluorophenyl
2	isoamyl	p-nitrophenyl
3	isoamyl	o-nitrophenyl
4	isoamyl	ß-naphthyl
5	isoamyl	2-thienyl
6	isoamyl	benzyl
7	isobutyl	p-fluorophenyl
8	p-fluorobenzyl	phenyl
9	4-pyridylmethyl	phenyl
10	cyclohexylmethyl	phenyl
11	allyl	phenyl
12	propyl	phenyl
13	cyclopropylmethyl	phenyl
14	methyl	phenyl
15	propargyl	phenyl
16	isoamyl	p-chlorophenyl

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TABLE 1A (Cont'd)
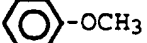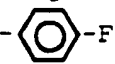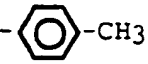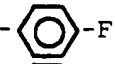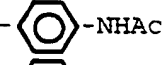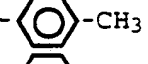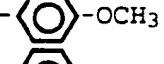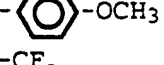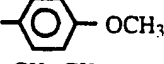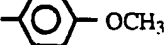
	Entry	R^3	R^4
5	17	isoamyl	p-methoxyphenyl
	18	isoamyl	m-nitrophenyl
	19	isoamyl	m-trifluoromethylphenyl
	20	isoamyl	o-methoxycarbonylphenyl
10	21	isoamyl	p-acetamidophenyl
	22	isobutyl	phenyl
	23	-CH$_2$Ph	-Ph
	24	-CH$_2$-(phenyl)-F	-Ph
	25	-CH$_2$-(cyclohexyl)	-Ph
15	26	-CH$_2$-(phenyl)-OCH$_3$	-Ph
	27	-CH$_2$-(pyridyl N)	-Ph
	28	-CH$_2$-(cyclopropyl)	-Ph
	29	-CH$_2$CH=CH$_2$	-Ph
	30	-(phenyl)	-Ph
20	31	-(cyclohexyl)	-Ph
	32	-CH$_2$CH$_2$Ph	-Ph
	33	-CH$_2$CH$_2$CH$_2$CH$_2$OH	-Ph
	34	-CH$_2$CH$_2$N(CH$_3$)$_2$	-Ph
	35	-CH$_2$CH$_2$-N(morpholino)O	-Ph
25	36	-CH$_3$	-Ph
	37	-CH$_2$CH$_2$CH$_2$SCH$_3$	-Ph
	38	-CH$_2$CH$_2$CH$_2$S(O)$_2$CH$_3$	-Ph
	39	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-(phenyl)
	40	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-CH$_2$CH$_2$CH$_3$

64

TABLE 1A (Cont'd)

Entry	R^3	R^4
41	$-CH_2CH_2CH(CH_3)_2$	$-CH_3$
42	$-CH_2CH_2CH(CH_3)_2$	$-C_6H_4-F$ (phenyl)
43	$-CH_2CH_2CH(CH_3)_2$	$-C_6H_4-CH_3$ (phenyl)
44	$-CH_2CH_2CH(CH_3)_2$	phenyl with CO_2CH_3
45	$-CH_2CH(CH_3)_2$	$-C_6H_4-F$ (phenyl)
46	$-CH_2CH(CH_3)_2$	$-C_6H_4-NHAc$ (phenyl)
47	$-CH_2CH(CH_3)_2$	$-C_6H_4-CH_3$ (phenyl)
48	$-CH_2CH_2CH_3$	$-C_6H_4-OCH_3$ (phenyl)
49	$-CH_2CH_2CH_2CH_3$	$-C_6H_4-OCH_3$ (phenyl)
50	$-CH_2CH_2CH(CH_3)_2$	$-CF_3$
51	$-CH_2CH(CH_3)_2$	$-CH_3$
52	$-CH_2CH_2CH(CH_3)_2$	$-CH_2Cl$
53	$-CH_2CH(CH_3)_2$	$-CH_2=CH-C_6H_5$ (phenyl)
54	$-CH_2CH(CH_3)_2$	$-C_6H_4-OCH_3$ (phenyl)
55	$-CH_2CH(CH_3)_2$	$-CH=CH_2$
56	$-CH_2-CH)CH_3)(CH_2CH_3)$	$-C_6H_4-OCH_3$ (phenyl)

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TABLE 1A (Cont'd)
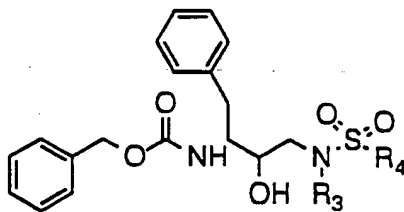
MASS MEASUREMENT

Entry	R³	R⁴	MOL FORM	CALC	FOUND
1	CH₂-CH(CH₃)-CH₃	—⬡—CH₃	$C_{29}H_{36}N_2O_5S$	531 (M+Li)	531
2		—⬡—OCH₃	$C_{29}H_{36}N_2O_6S$	541(M+H)	541
3		—⬡—OCH₂CH₃	$C_{30}H_{36}N_2O_6S$	555.2529 (M+H)	555.2582
4		—⬡—NO₂			
5		—⬡—Cl			
6		—⬡—F	$C_{28}H_{33}N_2O_5SF$	529.2172 (M+H)	521.2976
7		—⬡—CF₃			
8		—⬡—SCH₃	$C_{29}H_{36}N_2O_5S_2$	563 (M+Li)	563
9		—⬡—SOCH₃	$C_{29}H_{36}N_2O_6S_2$	573(M+H)	573
10		—⬡—SO₂CH₃	$C_{29}H_{36}N_2O_7S_2$	595 (M+Li)	595

5

66
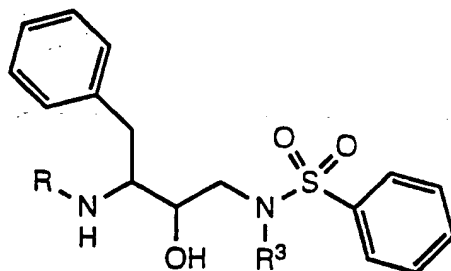
TABLE 1B

Entry	R	R³
1		-CH₂Ph
2		-CH₂CH₂CH(CH₃)₂
3		-CH₂CH(CH₃)₂
4		-CH₂CH(CH₃)₂
5		-CH₂CH(CH₃)₂

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TABLE 1B (Cont'd)
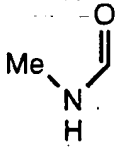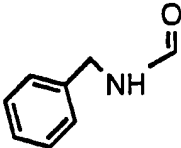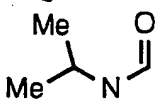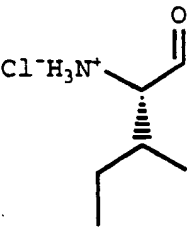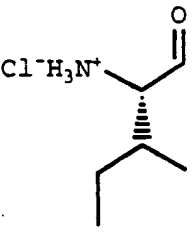
Entry	R	R^3
6	Me–NH–C(=O) (N-methylformamide)	$-CH_2CH(CH_3)_2$
7	PhCH2–NH–C(=O) (N-benzylformamide)	$-CH_2CH(CH_3)_2$
8	(Me)(Me)CH–N–C(=O) (N-isopropylformamide)	$-CH_2CH(CH_3)_2$
9	$Cl^- H_3N^+$ ... (aminoaldehyde, sec-butyl side chain)	$-CH_2CH_2(CH_3)_2$
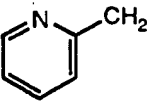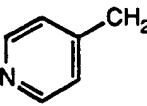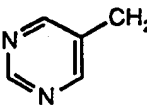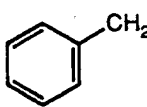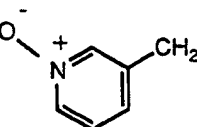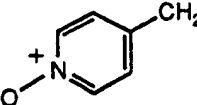
Table 1C

X	R^8	FORMULA	Mass Determination Calc	Found
H		$C_{27}H_{33}N_3O_5S$	512.2219(M+H)	521.2267
OCH$_3$		$C_{28}H_{35}N_3O_6S$	548.2407(M+Li)	548.2434
F		$C_{27}H_{32}N_3O_5SF$	530(M+H)	530
Cl		$C_{27}H_{32}N_3O_5SCl$	546(M+H)	546
NO$_2$		$C_{27}H_{32}N_4O_7S$	557(M+H)	557
OH		$C_{27}H_{33}N_3O_6S$	528(M+H)	528

TABLE 1C (Cont'd)

X	R^8	FORMULA	Mass Determination Calc	Found
OCH_3	(2-pyridyl)CH_2	$C_{28}H_{35}N_3O_6S$	542.2325(M+H)	542.2362
OCH_3	(4-pyridyl)CH_2	$C_{28}H_{35}N_3O_6S$	548.2407(M+Li)	548.2393
OCH_3	(5-pyrimidinyl)CH_2	$C_{28}H_{35}N_3O_6S$	543(M+H)	543
OCH_3	(phenyl)CH_2	$C_{29}H_{36}O_6N_2S$	547.2454(M+Li)	547.2475
OCH_3	tert-Butyl	$C_{26}H_{38}N_2O_6S$	513.2611(M+Li)	513.2593
OCH_3	(1-oxido-pyridin-3-yl)CH_2	$C_{28}H_{35}N_3O_7S$	564(M+Li)	564
OCH_3	(1-oxido-pyridin-4-yl)CH_2	$C_{28}H_{35}N_3O_7S$	564(M+Li)	564

The following Examples 7-9 illustrate
preparation of β-amino acid intermediates. These
intermediates can be coupled to the intermediate
compounds of Examples 1-6 to produce inhibitor compounds
5 of the present invention containing β-amino acids.

Example 7

A. Preparation of 4(4-methoxybenzyl)itaconate
10
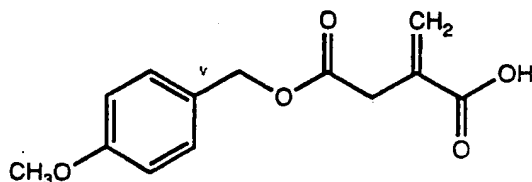
A 5 L three-necked round bottomed flask
equipped with constant pressure addition funnel, reflux
15 condenser, nitrogen inlet, and mechanical stirrer was
charged with itaconic anhydride (660.8g, 5.88 mol) and
toluene (2300 mL). The solution was warmed to reflux and
treated with 4-methoxybenzyl alcohol (812.4g, 5.88 mol)
dropwise over a 2.6h period. The solution was maintained
20 at reflux for an additional 1.5h and then the contents
were poured into three 2 L erlenmeyer flasks to
crystallize. The solution was allowed to cool to room
temperature whereupon the desired mono-ester
crystallized. The product was isolated by filtration on
25 a Buchner funnel and air dried to give 850.2g, 58% of
material with mp 83-85°C, a second crop, 17% was isolated
after cooling of the filtrate in an ice bath. ^{1}H NMR
(CDCl$_3$) 300 MHz 7.32(d, J=8.7 Hz, 2H), 6.91(d, J=8.7 Hz,
2H), 6.49(s, 1H), 5.85(s, 1H), 5.12(s, 2H), 3.83(s, 3H),
30 3.40(s, 2H).

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B. Preparation of Methyl 4(4-methoxybenzyl) itaconate
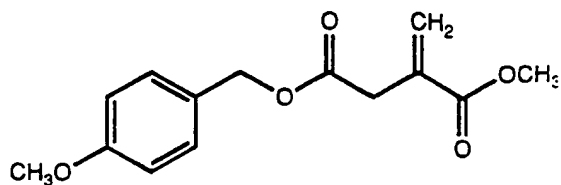
5   A 5 L three-necked round bottomed flask
equipped with reflux condenser, nitrogen inlet, constant
pressure addition funnel and mechanical stirrer was
charged with 4(4-methoxybenzyl) itaconate (453.4g, 1.81
mol) and treated with 1,5-diazabicyclo[4.3.0]non-5-ene
10 (275.6g, 1.81 mol), (DBN), dropwise so that the
temperature did not rise above 15°C. To this stirring
mixture was added a solution of methyl iodide (256.9g,
1.81 mol) in 250 mL of toluene from the dropping funnel
over a 45m period. The solution was allowed to warm to
15 room temperature and stirred for an additional 3.25h.

      The precipitated DBN hydroiodide was removed by
filtration, washed with toluene and the filtrate poured
into a separatory funnel. The solution was washed with
20 sat. aq. $NaHCO_3$ (2 X 500 mL), 0.2N HCl (1 X 500 mL), and
brine (2 X 500 mL), dried over anhyd. $MgSO_4$, filtered,
and the solvent removed in vacuo. This gave a clear
colorless oil, 450.2g, 94% whose NMR was consistent with
the assigned structure. ^1H NMR ($CDCl_3$) 300 MHz 7.30(d,
25 J=8.7 Hz, 2H), 6.90(d, J=8.7 Hz, 2H), 6.34(s, 1H),
5.71(s, 1H), 5.09(s, 2H), 3.82(s, 3H), 3.73(s, 3H),
3.38(s, 2H). ^{13}C NMR ($CDCl_3$) 170.46, 166.47, 159.51,
133.55, 129.97, 128.45, 127.72, 113.77, 66.36, 55.12,
51.94, 37.64.
30

C. Preparation of Methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate
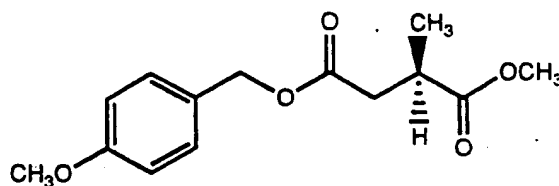
A 500 mL Fisher-Porter bottle was charged with methyl 4(4-methoxybenzyl) itaconate (71.1g, 0.269 mol), rhodium (R,R) DiPAMP catalyst (204mg, 0.269 mmol, 0.1 mol%) and degassed methanol (215 mL). The bottle was flushed 5 times with nitrogen and 5 times with hydrogen to a final pressure of 40 psig. The hydrogenation commenced immediately and after ca. 1h the uptake began to taper off, after 3h the hydrogen uptake ceased and the bottle was flushed with nitrogen, opened and the contents concentrated on a rotary evaporator to give a brown oil that was taken up in boiling *iso*-octane (ca. 200 mL, this was repeated twice), filtered through a pad of celite and the filtrate concentrated in vacuo to give 66.6g, 93% of a clear colorless oil, ^{1}H NMR (CDCl3 300 MHz 7.30(d, J=8.7 Hz, 2H), 6.91(d, J=8.7 Hz, 2H), 5.08(s, 2H), 3.82(s, 3H), 3.67(s, 3H), 2.95(ddq, J=5.7, 7.5, 8.7 Hz, 1H), 2.79(dd, J=8.1, 16.5 Hz, 1H), 2.45(dd, J=5.7, 16.5 Hz, 1H), 1.23(d, J=7.5 Hz, 3H).

D. Preparation of Methyl 2(R)-methylsuccinate

A 3 L three-necked round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer, reflux condenser and constant pressure addition funnel was charged with methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate (432.6g, 1.65 mol) and toluene (1200 mL). The stirrer was started and the solution treated with trifluoroacetic acid (600 mL) from the dropping funnel over 0.25h. The solution turned a deep purple color and the internal temperature rose to 45°C. After stirring

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for 2.25h the temperature was 27°C and the solution had
acquired a pink color. The solution was concentrated on
a rotary evaporator. The residue was diluted with water
(2200 mL) and sat. aq. NaHCO3 (1000 mL). Additional
NaHCO3 was added until the acid had been neutralized.
The aqueous phase was extracted with ethyl acetate (2 X
1000 mL) to remove the by-products and the aqueous layer
was acidified to pH=1.8 with conc. HCl. This solution
was extracted with ethyl acetate (4 X 1000 mL), washed
with brine, dried over anhyd. MgSO4, filtered and
concentrated on a rotary evaporator to give a colorless
liquid 251g, >100% that was vacuum distilled through a
short path apparatus cut 1: bath temperature 120°C @
>1mm, bp 25-29°C; cut 2: bath temperature 140°C @ 0.5mm,
bp 95-108°C, 151g, $[\alpha]_d$ @ 25°C=+1.38°C (c=15.475, MeOH),
$[\alpha]_d$ =+8.48°C (neat); cut 3: bath temperature 140°C, bp
108°C, 36g, $[\alpha]_d$ @ 25°C=+1.49°C (c=15.00, MeOH), $[\alpha]_d$
=+8.98°C (neat). Cuts 2 and 3 were combined to give
189g, 78% of product, ^{1}H NMR (CDCl3) 300 MHz 11.6(brs,
1H), 3.72(s, 3H), 2.92(ddq, J=5.7, 6.9, 8.0 Hz, 1H),
2.81(dd, J=8.0, 16.8 Hz, 1H), 2.47(dd, J=5.7, 16.8 Hz,
1H), 1.26(d, J=6.9 Hz, 3H).

E.   Preparation of Methyl Itaconate
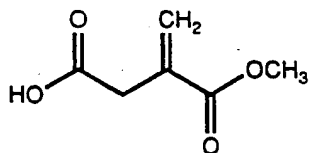
       A 50 mL round bottomed flask equipped with
reflux condenser, nitrogen inlet and magnetic stir bar
was charged with methyl 4(4-methoxybenzyl) itaconate
(4.00g, 16 mmol), 12 mL of touluene and 6 mL of
trifluoroacetic acid. The solution was kept at room
temperature for 18 hours and then the volatiles were
removed in vacuo. The residue was taken up in ethyl
acetate and extracted three times with saturated aqueous

sodium bicarbonate solution. The combined aqueous
extract was acidified to pH=1 with aqueous potassium
bisulfate and then extracted three times with ethyl
acetate. The combined ethyl acetate solution was washed

5   with saturated aqueous sodium chloride, dried over
anhydrous magnesium sulfate, filtered, and concentrated
in vacuo. The residue was then vacuum distilled to give
1.23g, 75% of pure product, bp 85-87 @ 0.1 mm. ^{1}H NMR
(CDCl$_3$) 300 MHz 6.34(s, 1H), 5.73(s, 2H), 3.76(s, 3H),

10   3.38(s, 2H). ^{13}C NMR (CDCl$_3$) 177.03, 166.65, 129.220,
132.99, 52.27, 37.46.

F.   Curtius Rearrangement of Methyl 2(R)-methylsuccinate:
15   Preparation of Methyl N-Moz-α-methyl β-alanine.
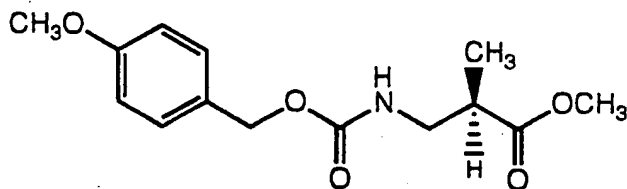
     A 5L four necked round bottomed flask equipped
20   with a nitrogen inlet, reflux condenser, mechanical
stirrer, constant pressure addition funnel, and
thermometer adapter was charged with methyl 2(R)-
methylsuccinate (184.1g, 1.26 mol), triethylamine
(165.6g, 218 mL, 1.64 mol, 1.3 equivalents), and toluene

25   (1063 mL). The solution was warmed to 85°C and then
treated dropwise with a solution of diphenylphosphoryl
azide (346.8g, 1.26 mol) over a period of 1.2h. The
solution was maintained at that temperature for an
additional 1.0h and then the mixture was treated with

30   4-methoxybenzyl alcohol (174.1g, 1.26 mol) over a 0.33h
period from the dropping funnel. The solution was
stirred at 88°C for an additional 2.25h and then cooled
to room temperature. The contents of the flask were
poured into a separatory funnel and washed with sat. aq.

35   NaHCO$_3$ (2 X 500 mL), 0.2N HCl (2 X 500 mL), brine (1 X

75

500 mL), dried over anhyd. MgSO4, filtered, and
concentrated in vacuo to give 302.3g, 85% of the desired
product as a slightly brown oil. 1H NMR (CDCl3) 300 MHz
7.32(d, J=8.4 Hz, 2H), 6.91(d, J=8.4 Hz, 2H), 5.2(brm,
5   1H), 5.05(s, 2H), 3.83(s, 3H), 3.70(s, 3H), 3.35(m, 2H),
2.70(m, 2H), 1.20(d, J=7.2 Hz, 3H).

G.   Hydrolysis of Methyl N-Moz-α-methyl β-alanine:
Preparation of α-methyl β-alanine Hydrochloride
10
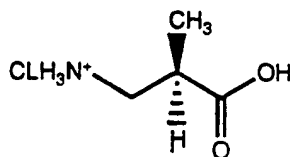
A 5 L three-necked round bottomed flask
equipped with a reflux condenser, nitrogen inlet and
15   mechanical stirrer was charged with methyl N-Moz-α-methyl
β-alanine (218.6g, 0.78 mol), glacial acetic acid (975
mL) and 12N hydrochloric acid (1960 mL). The solution
was then heated to reflux for 3h. After the solution had
cooled to room temperature (ca. 1h) the aqueous phase was
20   decanted from organic residue (polymer) and the aqueous
phase concentrated on a rotary evaporator. Upon addition
of acetone to the concentrated residue a slightly yellow
solid formed that was slurried with acetone and the white
solid was isolated by filtration on a Buchner funnel.
25   The last traces of acetone were removed by evacuation to
give 97.7g, 90% of pure product, mp 128.5-130.5°C [α]$_d$ @
25°C=9.0°C (c=2.535, Methanol). 1H NMR (D2O) 300 MHz
3.29(dd, J=8.6, 13.0 Hz, 1H), 3.16(dd, J=5.0, 13.0m Hz,
1H), 2.94(ddq, J=7.2, 5.0, 8.6 Hz, 1H), 1.30(d,J=7.2 Hz,
30   3H); 13C NMR (D2O) 180.84, 44.56, 40.27, 17.49.

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H. Preparation of N-Boc α-Methyl β-Alanine
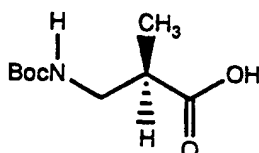
5   A solution of a-methyl b-alanine hydrochloride
(97.7g, 0.70 mol) in water (1050 mL) and dioxane (1050
mL) the pH was adjusted to 8.9 with 2.9N NaOH solution.
This stirring solution was then treated with di-*tert*-
butyl pyrocarbonate (183.3g, 0.84 mol, 1.2 equivalents)
10   all at once. The pH of the solution was maintained
between 8.7 and 9.0 by the periodic addition of 2.5N NaOH
solution. After 2.5h the pH had stabilized and the
reaction was judged to be complete. The solution was
concentrated on a rotary evaporator (the temperature was
15   maintained at <40°C). The excess di-*tert* -butyl
pyrocarbonate was removed by extraction with
dichloromethane and then the aqueous solution was
acidified with cold 1N HCl and immediately extracted with
ethyl acetate (4 X 1000 mL). The combined ethyl acetate
20   extract was washed with brine, dried over anhyd. MgSO$_4$,
filtered and concentrated on a rotary evaporator to give
a thick oil 127.3g, 90% crude yield that was stirred with
n-hexane whereupon crystals of pure product formed,
95.65g, 67%, mp 76-78°C, [α]$_d$ @ 25°C=-11.8°C (c=2.4,
25   EtOH). A second crop was obtained by concentration of
the filtrate and dilution with hexane, 15.4g, for a
combined yield of 111.05g, 78%. 1H NMR (acetone D$_6$) 300
MHz 11.7 (brs, 1H), 6.05 (brs 1H), 3.35 (m, 1H), 3.22 (m,
1H), 2.50 (m, 1H), 1.45(s, 9H), 1.19 (d, J=7.3 Hz, 3H);
30   13C NMR (acetone D$_6$) 177.01, 79.28, 44.44, 40.92, 29.08,
15.50. Elemental analysis calc'd. for C$_9$H$_{17}$NO$_4$: C,
53.19, H, 8.42; N, 6.89. Found: C, 53.36; H, 8.46; N,
6.99.

I.   Preparation of N-4-Methoxybenzyloxycarbonyl α-Methyl
β-Alanine

A solution of N-4-methoxybenzyloxycarbonyl
α-methyl β-alanine methyl ester (2.81g, 10.0 mmol) in 30
mL of 25% aqueous methanol was treated with lithium
hydroxide (1.3 equivalents) at room temperature for a
period of 2h. The solution was concentrated in vacuo and
the residue taken up in a mixture of water and ether and
the phases separated and the organic phase discarded.
The aqueous phase was acidified with aqueous potassium
hydrogen sulfate to pH=1.5 and then extracted three times
with ether. The combined ethereal phase was washed with
saturated aqueous sodium chloride solution, dried over
anhydrous magnesium sulfate, filtered and concentrated in
vacuo to give 2.60 g, 97% of N-4-Methoxybenzyloxycarbonyl
α-methyl β-alanine (N-Moz-AMBA) which was purified by
recrystallization from a mixture of ethyl acetate and
hexane to give 2.44g, 91% of pure product, mp 96-97°C,
MH+=268. ^{1}H NMR (D$_6$-acetone/300 MHz) 1.16 (3H, d,
J=7.2Hz), 2.70 (1H, m), 3.31 (2H, m), 3.31 (3H, s), 4.99
(2H, s), 6.92 (2H, 4, J=8.7 Hz), 7.13 (2H, d, J=8.7 Hz).

<u>Example 8</u>

Utilizing generally the procedure set forth in
Example 7, the following β-amino acid compounds were
prepared.

78
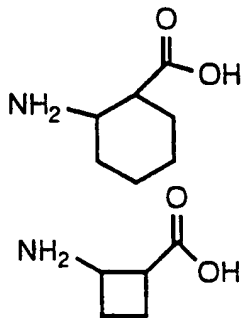
Example 9

Following generally the procedure of Example 7, the β-amino acids set forth in Table 2 were prepared.

Table 2

Entry	R^1	$R^{1'}$	$R^{1''}$
1	$-CH_3$	H	H
2	$-CH(CH_3)_2$	H	H
3	$-C(CH_3)_3$	H	H
4	H	H	H
5	H	$-CH_3$	H
6	H	$-CH_3$	$-CH_3$
7	H	H	$-CO2CH_3$
8	H	H	$-CONH_2$
9	$-CH_2CH_3$	H	H
10	$-CH_2CH(CH_3)_2$	H	H
11	$-CH_2C_6H_5$	H	H
12	$-CH_2$⬡OH	H	H
13	$-CH_2$⬡	H	H
14	$-CH_2COOH$	H	H
15	H	$-CH(CH_3)_2$	H
16	H	$-CH_2CH(CH_3)_2$	H
17	H	$-CH_2$⬡	H

79

Table 2 (Cont'd)

Entry	R^1	R$^1{}'$	R$^1{}''$
18	H	-CH$_2$CH$_2$ — (phenyl)	H
19	H	-(CH$_2$)$_3$ — (phenyl)	H
20	H	-(CH$_2$)$_4$ — (phenyl)	H
21	H	-(CH$_2$)$_3$CH(C$_6$H$_5$)$_2$	H

Example 10A
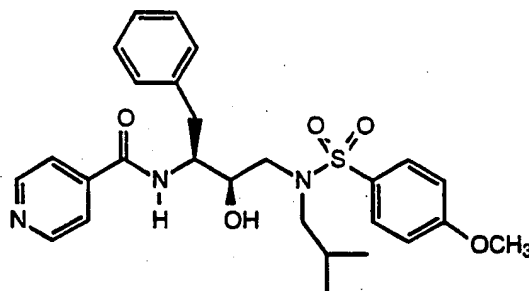
Preparation of 4-Pyridinecarboxamide,
N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]

To a solution of 231 mg (0.57 mmol) of 2R-
hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]
amino-1S-(phenylmethyl)propylamine in 3 mL of methylene
chloride at 0 C, was added 288 mg(2.85 mmol) of
triethylamine and then 112 mg(0.63 mmol) of isonicotinoyl
chloride hydrochloride. After 19 hours at room
temperature, the solvent was removed, ethyl acetate
added, then washed with saturated sodium bicarbonate,
brine, dried with magnesium sulfate, filtered and
concentrated to afford 290 mg of crude product. This was
chromatographed on silica gel using 3-5%
isopropanol/methylene chloride as eluent to afford 190 mg

80

of the desired compound; mass spectrum calc. for
C27H34N3O5S (M + H) 512.2219; found 512.2280.

Example 10B
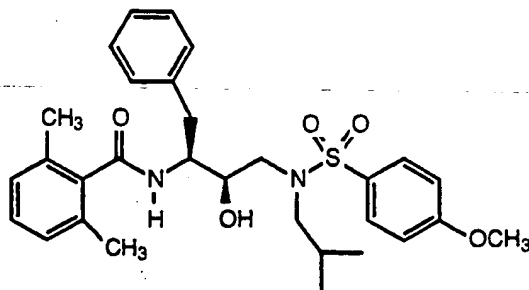
Preparation of Benzamide,
N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-2,6-dimethyl

To a solution of 83 mg (0.55 mmol) of 2,6-
dimethylbenzoic acid and 125 mg (0.82 mmol) of N-
hydroxybenzotriazole in 3 mL of anhydrous DMF at 0 C was
added 117 mg (0.61mmol) of 1-(3-dimethylaminopropyl)-3-
ethylcarbodiimide hydrochloride. After 2 hours at 0 C,
203 mg (0.50 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-
methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
was added. After 22 hours at room temperature, the
solvent was removed in vacuo, ethyl acetate added, then
washed with saturated sodium bicarbonate, brine, dried
over magnesium sulfate, filtered and concentrated to
afford 300 mg of crude product. Chromatography on silica
gel using 20-50% ethyl acetate/hexane afforded 37 mg of
the desired product; mass spectrum calcd for C30H38N2O5S
(M+H) 539.2580; found 539.2632.
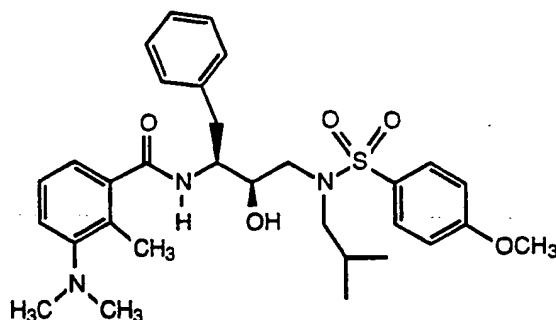
81

Example 10C

Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2-methyl.

Part A. Preparation of 4-Nitro-2-methylbenzoic Acid.

A mixture of 1.0 g (3.8 mmol) of 2-iodo-nitrotoluene, 2.1
g (15.2 mmol) potassium carbonate and 27 mg (0.038 mmol)
of palladium(II) dichloride bis(triphenylphosphine) in a
mixture of 5mL of water and 10 mL of N,N-
dimethylformamide. This was placed in a Fisher/Porter
bottle under 15 psig of carbon monoxideand heated at 70°C
for 16 hours. The solution became homogeneous when
heated. The reaction was cooled, diethyl ether and water
was added, the organic layer separated and discarded.
The aqueous layer was acidified with 1N hydrohloric acid,
extracted with ethyl acetate, washed with water, brine,
dried over magnesium sulfate, filtered and concentrated
to yield 0.5g of crude material. This dissolved in ethyl
acetate, hexane added and the resulting brown solid
discarded. The filtrate was concentrated, and then
recrystallized fom diethyl ether/hexane to afford 215mg
of 4-nitro-2-methylbenzoic acid, m/e=182(M+H).

Part B. Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2-methyl-4-nitro.

To a solution of 181mg (1.0mmol) of 4-nitro-2-
methylbenzoic acid and 230mg(1.5mmol) N-
hydroxybenzotriazole in 3mL of anhydrous N,N-
5   dimethylformamide at 0°C, was added 211mg(1.1mmol) of 1-
(3-dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride. After stirring at 0 C for 1 hour, 406mg
(1mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-
methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
10   was added. After 17 hours at room temperature, the
solvent was removed under reduced pressure, ethyl acetate
added, washed with 5% citric acid, saturated sodium
bicarbonate, brine, dried with magnesium sulfate,
filtered and concentrated to yield 0.55g of crude
15   product. This was chromatographed on silica gel using
20-50% ethyl acetate/hexane as eluent to afford 0.49g of
the desired benzamide, N-[2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2-methyl-4-nitro, m/e=570(M+H).
20

Part C. Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2-methyl-4-amino.

25   A solution of 400mg (0.70mmol) of benzamide, N-[2R-
hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-
nitro from part B in 20mL of methanol was hydrogenated
over 0.2 g of 10% palladium on carbon catalyst under 50
30   psig of hydrogen for 2.5 hours. The catalyst was removed
by filtration and the solution concentrated to afford
370mg of the desired benzamide, N-[2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2-methyl-4-amino, m/e=540(M+H).
35

Part D. Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2-methyl-4-dimethylamino.

83

A solution of 0.17g (0.31mmol) of benzamide, N-[2R-
hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-
5   amino from part C in 5mL of methanol and 0.20mL of 37%
aqueous formaldehyde was hydrogenated over 90mg of 10%
palladium on carbon under 15psig of hydrogen for 16
hours. The catalyst was removed by filtration, the
solvents removed under reduced pressure to afford 0.16g
10 of crude material. Chromatography on silica gel using
50% ethyl acetate as eluent afforded 0.12g of the desired
benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl]
(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-
4-dimethylamino, m/e=568(M+H).

15

<u>Example 10D</u>
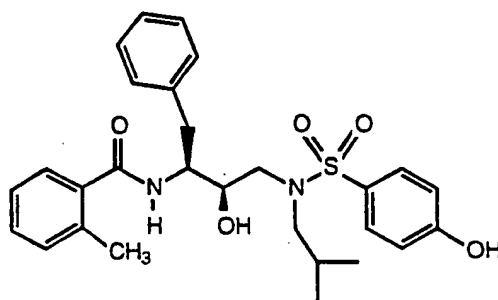
20 <u>Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-
    hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
    (phenylmethyl)propyl]-2-methyl.</u>

To a solution of 500 mg (1mmol) of 2R-hydroxy-3-[(2-
25 methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-
(phenylmethyl)propylamine in 2 mL of methylene chloride
and 2 mL of N,N-dimethylformamide, was added 0.42 mL of
triethylamine, followed by 0.12 mL of ortho-toluoyl
chloride. After 17 hours, the solvent was removed under
30 reduced pressure, the residue dissolved in ethyl acetate,
was with 5% citric acid, saturated sodium bicarbonate and
brine, dried over anhydrous magnesium sulfate, filtered

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and concentrated to afford 490 mg of crude material.
This was chromatographed over 100g of silica gel using
20-50% ethyl acetate/hexane as eluent to afford 232 mg of
the desired product, m/e=511(M+H).

5

Example 10E
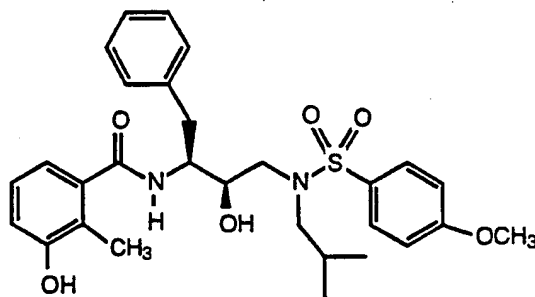
10   Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-
      methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
      (phenylmethyl)propyl]-3-hydroxy-2-methyl

      To a solution of 131 mg (0.86 mmol) of 3-hydroxy-2-
15   methylbenzoic acid and 305 mg (0.75 mmol) of N-
      hydroxybenzotriazole in 4 mL of anhydrous N,N-
      dimethylformamide at 0°C, was added 165 mg (0.86 mmol) of
      EDC. After 20 minutes of activation at 0°C and 1 hour at
      room temperature, 305 mg (0.75 mmol) of 2R-hydroxy-3-[(2-
20   methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-
      (phenylmethyl)propylamine was added. After 15 hours at
      room temperature, ethyl acetate was added, washed with 5%
      citric acid, saturated sodium bicarbonate, brine, dried,
      filtered and concentrated to afford 460 mg of crude
25   material. This was chromatographed on silica gel using
      0-35% ethyl acetate/methylene chloride as eluent to
      afford 250 mg of pure benzamide, N-[2R-hydroxy-3-[[(4-
      methoxyphenyl)sulfonyl] (2-methylpropyl)amino]-1S-
      (phenylmethyl)propyl]-3-hydroxy-2-methyl, m/e =
30   547(M+Li).

85

Example 10F
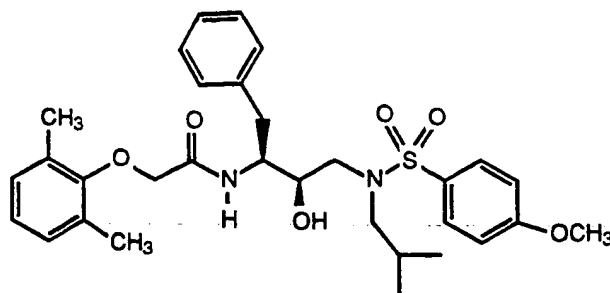
5   Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl)
    sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-
    (2,6-dimethylphenoxy)acetamide

    Part A: Preparation of 2,6-Dimethylphenoxyacetic acid
10
    2,6-Dimethylphenol (6.1 g, 50.0 mmol), bromoacetic acid
    (6.9 g, 50.0 mmol) and 2.5 N aqueous sodium hyroxide
    (50.0 mL, 125.0 mmol) were refluxed in water (125 mL) for
    4 hrs. Bromoacetic acid (6.9 g, 50.0 mmol) and 2.5 N
15 aqueous sodium hydroxide (20.0 mL, 62.5 mmol) were added
    and the solution refluxed for an additional 16 hrs. The
    solution was cooled to room temperature and water (200
    mL) was added. The pH of the solution was adjusted to
    1.0 with concentrated aqueous hydrochloric acid. The
20 resulting precipitate was collected and recrystallized
    from ethyl acetate/hexanes (1:9, 700 mL). 2,6-
    Dimethylphenoxyacetic acid (4.53 g, 25.1 mmol, 50%) was
    collected as a white crystalline solid. ^{1}H NMR (CD$_3$OD) d
    2.26 (s, 6H), 4.38 (s, 2H), 6.90-7.00 (m, 3H).
25
    Part B: Preparation of N-[2R-hydroxy-3-[[(4-
    methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
    (phenylmethyl)propyl]-(2,6-dimethylphenoxy)acetamide

30 To a solution of 180.1 mg (0.83 mmol) of 2,6-
    (dimethylphenoxy)acetic acid in 10 mL of anhydrous
    methylene chloride at room temperature, was added 114 mg

(0.60 mmol) of EDC. After 15 minutes of activation, 203 mg of 2R-hydroxy-3-[[(2-methylpropyl)(4-methoxybenzene) sulfonyl]amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 16 hours the

5   solution was extracted with 5% citric acid, sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 244 mg of crude product. A quantity of this (15 mg) was chromatographed on silica gel using 25% ethyl acetate/hexane to afford 8

10 mg of the desired compound, m/e=575(M+Li).

<div align="center">Example 10G</div>
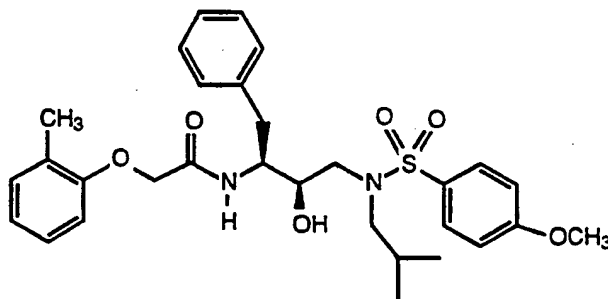
15

Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-(2-methylphenoxy)acetamide

20 Part A: Preparation of 2-Methylphenoxyacetic Acid.

2-Methylphenol (2.0 g, 18.4 mmol), bromoacetic acid (2.5 g, 18.4 mmol) and 2.5 N aqueous sodium hyroxide (25.0 mL, 62.55.0 mmol) refluxed for 16 hrs. The pH of the

25 solution was adjusted to 1 with concentrated aqueous hydrochloric acid. The resulting precipitate was collected triturated with hexanes. The 2-methylphenoxyacetic acid (720 mg, 4.33 mmol, 25%) was collected as a white crystalline solid. ^{1}HNMR (CD$_3$OD) d

30 2.43 (s, 3H), 4.65 (s, 2H) 6.70-7.10 (m, 4H).

87

Part B: Preparation of N-[2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-(2-methylphenoxy)acetamide

To a solution of 97 mg (0.59 mmol) of 2-(methylphenoxy)
acetic acid in 5 mL of anhydrous methylene chloride at
room temperature, was added 89.1 mg (0.55 mmol) of
carbonyl diimidazole. After 15 minutes of activation,
200 mg (0.49 mmol) of 2R-hydroxy-3-[[(2-methylpropyl)(4-
methoxybenzene)sulfonyl]amino]-1S-(phenylmethyl)
propylamine was added. After stirring at room
temperature for 15 hours the solution was extracted with
5% citric acid, sodium bicarbonate, brine, dried over
magnesium sulfate, filtered and concentrated to afford
crude product. This was chromatographed on silica gel
using 25% ethyl acetate/hexane to afford 198 mg of the
desired compound.

Example 10H
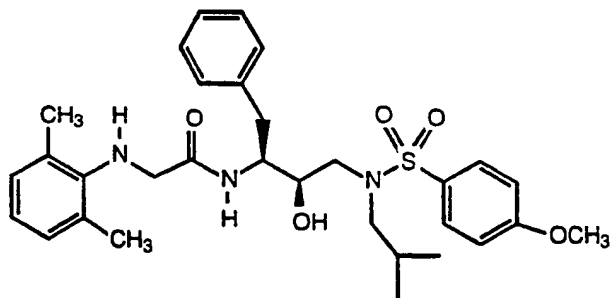
Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl)
sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-
2-(2,6-dimethylphenylamino)acetamide

Part A: Preparation of N-(2,6 Dimethylphenyl)glycine.

2,6-Dimethylaniline (6.1 g, 50.4 mmol), and ethyl
bromoacetate (8.4 g, 50.4 mmol) were refluxed neat for 10
min. The reaction mixture was cooled to room temperature
and poured into dichloromethane (75 mL). A precipitated

88

formed which was collected and triturated with dichloromethane (25 mL). N-(2,6-Dimethylphenyl)glycine hydrobromide salt (1.21 g, 4.6 mmol, 9.0%) was collected as a white crystalline solid. ^{1}H NMR (CD$_3$OD) d 2.48 (s,

5 6H), 4.29 (s, 2H), 7.00-7.10 (m, 3H).

Part B: Preparation of N-[2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2-(2,6-dimethylphenylamino)

10 acetamide

To a solution of 100 mg (0.39 mmol) of N-(2,6-
dimethylphenyl)glycine hydrobromide and 100 mg of
triethylamine in 5 mL of anhydrous methylene chloride at

15 room temperature, was added 74 mg (0.39 mmol) of EDC.
After 15 minutes of activation, 157 mg (0.39 mmol) of 2R-
hydroxy-3-[[(2-methylpropyl)(4-methoxybenzene)sulfonyl]
amino]-1S-(phenylmethyl)propylamine was added. After
stirring at room temperature for 4 hours, an additional

20 100 mg of N-(2,6-dimethylphenyl)glycine and 74 mg of EDC
was added. After stirring at room temperature for 16
hours, the solution was extracted with 5% citric acid,
sodium bicarbonate, brine, dried over magnesium sulfate,
filtered and concentrated to afford 206 mg of crude

25 product. This was purified by chromtaograpghy on reverse
phase using 20-90% acetonitrile/water (0.05%
trifluoroacetic acid) to afford 75 mg of the desired
compound, m/e = 568 (M+H).

30 Example 101
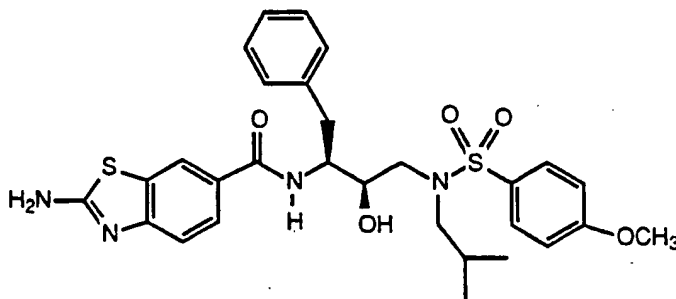
89

Preparation of N-[2R-hydroxy-3-[[(4-methoxyphenyl)
sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-
2-amino-benzothiazole-6-carboxamide

5

Part A: Preparation of 2-Amino-6-Carboxy-Benzothiazole
Ethyl Ester

A 100 ml round bottom flask equipped with magnetic stir

10   bar and N2 inlet was charged with 1.0 g of methyl p-
aminobenzoate in 35 mL methanol. The solution was heated
to reflux and 4.0 g of $Cu^{II}SO_4$ and 5.0 g of KSCN were
added. The reaction mixture was refluxed 2 hours and
then filtered. The filtrate was diluted with 60 mL of

15   water and 20 mL of ethanol and heated to boiling. Upon
cooling 1.15 g (78%) of 2-Amino-6-Carboxy-Benzothiazole
Ethyl Ester was isolated, m/e=223(M+H).

Part B: Preparation of 2-Amino-6-Carboxy-Benzothiazole.

20

A 50 mL round bottom flask equipped with magnetic stir
bar was charged with 250 mg 2-Amino-6-Carboxy-
Benzothiazole Ethyl Ester, 190 mg (4 eq.) LiOH in 3 mL
dioxane and 3 mL water. The slurry was heated to 60°C

25   for 2 hours. After 2 hours the solution was acidified
with 1N HCl and concentrated in vacuo to a light grey
solid which was identified as 2-amino-6-carboxy-
benzothiazole, m/e = 195(M+H). It was used without
further purification.

30

Part C: Preparation of N-[2R-hydroxy-3-[[(4-
methoxyphenyl) sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2-amino-benzothiazole-6-carboxamide

35   A 100 mL round bottom flask equipped with magnetic stir
bar and N2 inlet was charged with 110 mg 2-amino-6-
carboxybenzothiazole, 110 mg EDC, and 100 mg HOBt in 4 mL
dry DMF. After 30 minutes activation 203 mg amine (A)

and .5 mL of triethylamine were added and the reaction
was stirred overnight. The reaction was partioned
between ethyl acetate and saturated aqueous sodium
bicarbonate. The combined organics were washed with 10 %
5   aqueous Citric Aacid, water, saturated aqueous sodium
bicarbonate, brine and concentrated in vacuo to 210 mg
white foam, idenitifed as the desired product,
m/e=589 (M+Li)

10   Example 11A
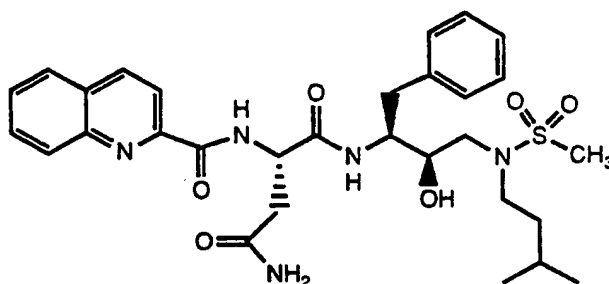
Preparation of N1-[2R-hydroxy-3-[(3-methylbutyl)(methyl-
15   sulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-
quinolinylcarbonyl)amino]butanediamide

Part A:

A solution of phenylmethyl [2R-hydroxy-3-[(3-
20   methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)-
propyl]carbamate prepared as in Example 3 (100 mg) in
methanol (10 mL) was hydrogenated over 10% palladium on
carbon for 2 hours, filtered through diatomaceous earth
and concentrated to give the product as an oil.

25

Part B:

A solution of N-CBZ-L-asparagine (61 mg,
0.23 mmol) and N-hydroxybenzotriazole (33 mg, 0.22 mmol)
in DMF (2 mL) was cooled to 0° C with an ice bath and
30   then EDC (42 mg, 0.22 mmol) was added. The solution was
stirred for 30 minutes at 0° C and then the product of
Part A (69 mg, 0.21 mmol) in DMF (2 mL) was added. After

30 minutes at 0° C the reaction was allowed to warm to
room temperature and stir for 16 hours. The reaction
mixture was then poured into a 50% saturated aqueous
solution of sodium bicarbonate (100 mL) and the resulting
5   white precipitate collected by suction filtration, washed
with water and dried *in vacuo*. The phenylmethyl
[3-amino-1S-[[2R-hydroxy-3-[(3-methylbutyl)
(methylsulfonyl)amino]-1S-(phenylmethyl)amino]carbonyl]-
3-oxopropyl]carbamate was obtained as a white solid Anal.
10   Calcd. for $C_{28}H_{40}N_4O_7S \cdot 0.5 H_2O$: C, 57.42; H, 7.06; N,
9.57. Found: C, 57.72; H, 7.21; N, 9.24.

Part C:

A solution of phenylmethyl [3-amino-1S-[[2R-
15   hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-
(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate
(135 mg, 0.23 mmol) in methanol (15 mL) was hydrogenated
over 10% palladium on carbon for 6 hours, filtered
through diatomaceous earth and concentrated to give the
20   product as an oil.

Part D:

To a solution of the product from Part C (101
mg, 0.23 mmol) in DMF (5 mL) was added 2-quinoline
25   carboxylic acid N-hydroxysuccinimide ester (67 mg, 0.25
mmol). The reaction was stirred at room temperature for
16 hours, then poured into a 50% saturated solution of
sodium bicarbonate (60 mL). The resulting solid was
collected by suction filtration washed with water and
30   dried *in vacuo*. The N1-[2R-hydroxy-3-[(3-methylbutyl)
(methylsulfonyl)-amino]-1S-(phenylmethyl)propyl]-2S-[(2-
quinolinylcarbonyl)-amino]butanediamide was obtained as a
white solid Anal. Calcd. for $C_{30}H_{39}N_5O_6S \cdot 0.1 H_2O$: C,
58.52; H, 6.71; N, 11.37. Found: C, 58.34; H, 6.35; N,
35   11.13.
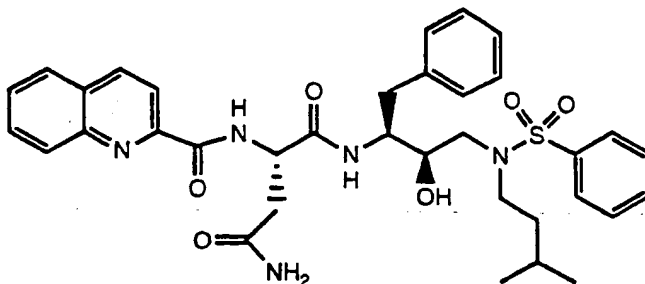
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Example 11B

Preparation of N1- [2R-hydroxy-3-[(3-methylbutyl)
(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-
quinolinylcarbonyl)amino]butanediamide.

Part A:

The CBZ protected compound phenylmethyl [2R-
hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]carbamate (200 mg, 0.38 mmol) was
deprotected by hydrogenation over 10% palladium on carbon
and the resulting product obtained as an oil.

Part B:

The free amine from Part A was coupled with
N-CBZ-L-asparagine (109 mg, 0.41 mmol) in the presence of
N-hydroxybenzotriazole (63 mg, 0.41 mmol) and EDC (77 mg,
0.40 mmol) to give phenylmethyl [3-amino-1S-[[2R-hydroxy-
3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate as a
white solid. Anal. Calcd. for $C_{33}H_{42}N_4O_7S$: C, 62.05; H,
6.63; N, 8.77. Found: C, 61.86; H, 6.60; N, 8.64.

Part C:

The product of Part B (110 mg, 0.17 mmol) was
deprotected by hydrogenation over 10% palladium on carbon
to give the product as an oil.

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Part D:

The resulting free amine was coupled with
2-quinoline carboxylic acid N-hydroxysuccinimide ester
(45 mg, 0.17 mmol) to give N1- [2R-hydroxy-3-[(3-
5   methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)
propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide as
a white solid. Anal. Calcd .for $C_{35}H_{41}N_5O_6S$: C, 63.71;
H, 6.26; N, 10.61. Found: C, 63.59; H, 6.42; N, 10.42.

10   Example 12A
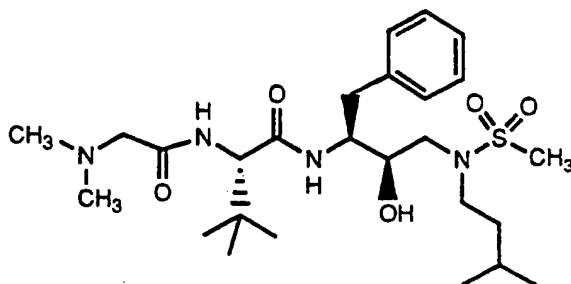
Preparation of 2S-[[(dimethylamino)acetyl]amino]-N-[2R-
15   hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3,3-dimethylbutanamide

Part A:

To a solution of N-CBZ-L-tert-leucine (100 mg,
20   0.38 mmol) and N-hydroxybenzotriazole (52 mg, 0.34 mmol)
in DMF (3 mL) was added EDC (65 mg, 0.34 mmol). The
solution was stirred for 60 minutes at room temperature
and then the product of Example 10, Part A (105 mg, 0.32
mmol) in DMF (2 mL) was added. The reaction was stirred
25   for 16 hours at room temperature, then poured into a 50%
saturated solution of sodium bicarbonate (50 mL). The
aqueous mixture was extracted twice with ethyl acetate
(25 mL). The combined ethyl acetate layers were washed
with water (25 mL) and dried over magnesium sulfate.
30   Filtration and concentration produced an oil which was
chromatographed on silica gel (50 gm) eluting with 2.5 %
methanol in dichloromethane. The phenylmethyl [1S-[[[2R-

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hydroxy-3-[(3-methylbutyl)-(methylsulfonyl)amino]-1S-
(phenylmethyl)propyl]amino]-carbonyl]-2,2-
dimethylpropyl]carbamate was obtained as a gummy solid
Anal. Calcd. for $C_{30}H_{45}N_3O_6S$ ◊ 2.2 H_2O: C, 58.55; H,
5   8.09; N, 6.83. Found: C, 58.38; H, 7.77; N, 7.10.

Part B:

A solution of phenylmethyl [1S-[[[2R-hydroxy-3-
[(3-methylbutyl)(methylsulfonyl)amino]-1S-
10   (phenylmethyl)propyl]amino]carbonyl]-2,2-
dimethylpropyl]carbamate (100 mg, 0.17 mmol) in methanol
(10 mL) was hydrogenated over 10% palladium on carbon for
2 hours. The reaction was filtered through diatomaceous
earth and concentrated to an oil.

15

Part C:

N,N-dimethylglycine (20 mg, 0.19 mmol),
N-hydroxybenzotriazole (28 mg, 0.18 mmol) and EDC (35 mg,
20   0.18 mmol) were stirred in DMF (4 mL) at room temperature
for 40 minutes. The product from Part B in DMF (4 mL)
was added and the reaction mixture stirred for 16 hours,
then poured into a 50% saturated sodium bicarbonate
solution (50 mL). The aqueous mixture was extracted
25   three times with dichloromethane (30 mL) which in turn
were washed with water (30 mL) and dried over magnesium
sulfate. Filtration and concentration afforded an oil.
The oil was chromatographed on silica gel (50 gm) eluting
initially with 2.5 % methanol in dichloromethane (400 mL)
30   and then with 5% methanol in dichloromethane. The 2S-
[[(dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-
methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)-
propyl]-3,3-dimethylbutanamide was obtained as a white
solid Anal. Calcd. for $C_{26}H_{46}N_4O_5S$ ◊ 0.5 CH_2Cl_2: C,
35   56.04; H, 8.34; N, 9.87. Found: C, 56.06; H, 8.36; N,
9.70.

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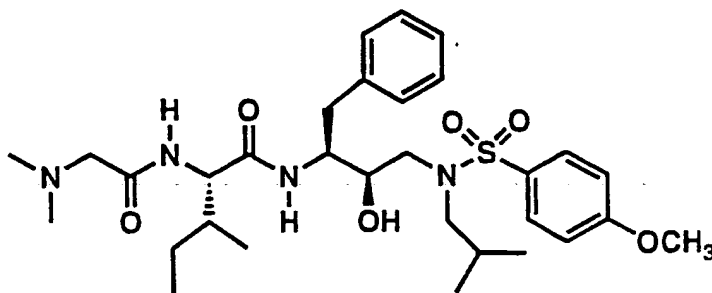## Example 12B
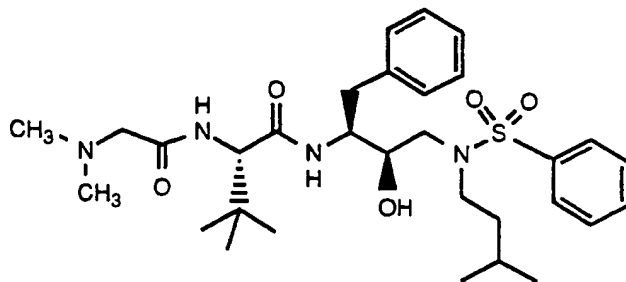
5 Preparation of 2S-[[(dimethylamino)acetyl]amino]-N-[2R-
hydroxy-3-[(3-methyl- butyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3,3-dimethylbutaneamide

Part A:

10

    To a solution of N-CBZ-L-tert-leucine (450 mg,
1.7 mmol) and N-hydroxybenzotriazole (260 mg, 1.7 mmol)
in DMF (10 mL) was added EDC (307 mg, 1.6 mmol). The
solution was stirred for 60 minutes at room temperature
15 and then the product of Example 11, Part A (585 mg, 1.5
mmol) in DMF
(2 mL) was added. The reaction was stirred for 16 hours
at room temperature, then poured into a 50% saturated
solution of sodium bicarbonate (200 mL). The aqueous
20 mixture was extracted thrice with ethyl acetate (50 mL).
The combined ethyl acetate layers were washed with water
(50 mL) and saturated NaCl solution (50 mL), then dried
over magnesium sulfate. Filtration and concentration
produced an oil which was chromatographed on silica gel
25 (50 gm) eluting with 20% ethyl acetate in hexane. The
phenylmethyl [1S-[[[2R-hydroxy-3-[(3-methylbutyl)
(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]
carbonyl]-2,2-dimethylpropyl]carbamate was obtained as a
solid Anal. Calcd for $C_{35}H_{47}N_3O_6S$: C, 65.91; H, 7.43; N,
30 6.59. Found: C, 65.42; H, 7.24; N, 6.55.

Part B:

A solution of phenylmethyl [1S-[[[2R-hydroxy-3-
[(3-methylbutyl)(phenylsulfonyl)-amino]-1S-
5   (phenylmethyl)propyl]amino]carbonyl]-2,2-
dimethylpropyl]carbamate (200 mg, 0.31 mmol) in methanol
(15 mL) was hydrogenated over 10% palladium on carbon for
2 hours. The reaction was filtered through diatomaceous
earth and concentrated to an oil.

10

Part C:

The resulting free amine from part B (150 mg,
0.3 mmol) was combined with diisopropylethylamine (114
15 uL, 0.33 mmol) in dichloromethane (5 mL). To this was
added bromoacetyl chloride (27 uL, 0.33 mmol) dropwise.
The reaction was stirred for 30 minutes at room
temperature, then diluted with dichloromethane (30 mL)
and extracted with 1 N HCl, water, and then saturated
20 NaCl solution (25 mL each). The organic solution was
dried over MgSO$_4$ and concentrated to a solid. The 2S-
[[bromoacetyl]amino]-N-[2R-hydroxy-3-[(3-
methylbutyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3,3-dimethylbutaneamide was
25 sufficiently pure for use in the next step. This
material can also be prepared by substituing bromoacetic
anhydride for bromoacetyl chloride, or one can use
chloroacetyl chloride or chloracetic anhydride.

30 Part D:

The product from part C was dissolved in
dichloromethane (5 mL) and diisopropylethylamine (114 uL,
0.66 mmol) and dimethylamine hydrochloride (53 mg, 0.66
35 mmol) were added. The reaction was stirred for 18 hours
then concentrated under a stream of nitrogen to about 1
mL. The residue was chromatographed on silica gel (50
gm) using 2% methanol in dichloromethane. The

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2S-[[(dimethylamino)-acetyl] amino]-N-[2R-hydroxy-3'-
[(3methylbutyl)-(phenylsulfonyl)amino]-1S-(phenylmethyl)
propyl]-3,3-dimethylbutaneamide was obtained as a solid.
Anal. Calcd for $C_{31}H_{48}N_4O_5S$: C, 63.24; H, 8.22; N, 9.52.
5   Found: C, 63.03; H, 8.01; N, 9.40.

Example 12C

10
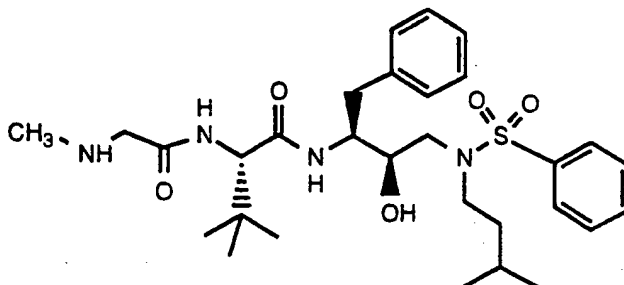
Preparation of 2S-[[(methylamino)acetyl]amino]-N-[2R-
hydroxy-3-[(3-methyl- butyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3,3-dimethylbutaneamide

15

        2S-[[bromoacetyl]amino]-N-[2R-hydroxy-3-[(3-
methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)
propyl]-3,3-dimethylbutaneamide (103 mg, 0.16 mmol) and
40% aqueous methylamine (42 uL, 0.49 mmol) were combined
20   in ethanol (2 mL) and stirred at room temperature for 24
hours. The reaction mixture was concentrated to dryness
and triturated with ether. The solid material was
removed by filtration and the filtrate concentrated to an
oil. The oil was chromatographed on silica (50 gm) using
25   4% methanol in dichloromethane. The 2S-[[(methylamino)
acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)
(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-
dimethylbutaneamide was obtained as a solid. Anal.
Calcd for $C_{30}H_{46}N_4O_5S$: C, 62.69; H, 8.07; N, 9.75. Found:
30   C, 62.38; H, 8.14; N, 9.60.

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Example 12D

Preparation of Pentanamide, 2S-[[(dimethylamino))acetyl]
amino]-N-[2R-hydroxy-3-[(3-methylbutyl)phenylsulfonyl)
amino]-1S-(phenylmethyl)propyl]3S-methyl-

Part A:

To a solution the amine product of Example 11,
Part A; (2.79 g, 7.1 mmol) in 27 mL of dioxane was added
(2.3 g, 7.1 mmol) of N-t-butylcarbonyl-L-isoleucine-N-
hydroxysuccinamide ester, and the reaction was stirred
under nitrogen atmosphere for 16 hours. The contents of
the reaction were concentrated in vacuo, and the residue
dissolved in ethyl acetate, washed with potassium
hydrogen sulfate (5% aqueous), saturated sodium
bicarbonate, and saturated sodium chloride. The organic
layer was dried over magnesium sulfate, filtered and
concentrated to yield 4.3 grams of crude material which
was chromatographed using 3:1 ethyl acetate: hexane to
obtain 3.05g, 72% yield of Pentanamide, 2S-[[(1,1-
dimethylethoxy)carbonyl]amino]-N-[2R-hydroxy-3-[(3-
methylbutyl)phenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3-methyl-.

Part B

(3.05g, 5.0 mmol) of the product from Part A
was dissolved in 20 mL of 4N HCl in dioxane and stirred
under nitrogen atmosphere for 1.5 hours. The contents
were concentrated in vacuo, and chased with diethyl

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ether. The crude hydrochloride salt was pumped on at 1
mm Hg until dry to yield 2.54 g of product as its
hydrochloride salt.

5   Part C:

         (2.54 g, 5.0 mmol) of amine hydrochloride was
dissolved in 50 mL of tetrahydrofuran and to this was
added (1.01 g, 10 mmol) of 4-methyl-morpholine, at which
time a precipitate forms. To this suspension was added
10   chloroacetic anhydride (0.865 g, 5.0 mmol) and stirred
for 40 minutes. The contents were concentrated in vacuo,
and the residue partitioned in ethyl acetate (200 mL) and
5% KHSO$_4$. The organic layer was washed with saturated
sodium bicarbonate, and saturated sodium chloride, dried
15   over magnesium sulfate, filtered and concentrated to
yield the crude product. Purification by silica gel
chromatography using an eluant of 1:1 ethyl acetate:
hexanes yielded 1.89 grams of pure chloroacetamide.

20   Part D:

         To a solution of chloroacetamide (1.89 g, 3.2
mmol) from Part C, in 25 mL of tetrahydrofuran was added
4.0 mL of 50% aqueous dimethylamine and the solution was
stirred for 1 hour. The solution was concentrated in
25   vacuo and the residue was dissolved in ethyl acetate and
washed with water. The organic layer was dried over
magnesium sulfate, filtered and concentrated to yield the
crude product which was purified by crystallization from
ethyl acetate and isooctane to yield 1.80 g, (88% yield),
30   mp. = 121-122 C, HRes. MS. calc. 589.3424, found
589.3405.

100

Example 12E
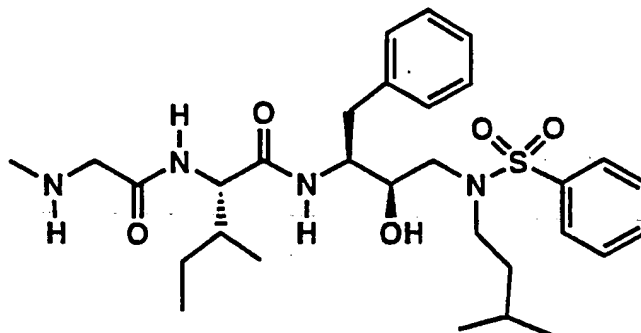
5   Preparation of Pentanamide, 2S-
     [[(Methylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-
     methylbutyl)(phenylsulfonyl)amino]-1S-
     (phenylmethyl)propyl]-3S-methyl-

10   To a solution of the chloroacetamide of Example
     12D, Part C, (2.36 g, 4.0 mmol) in tetrahydrofuran (25
     mL) was added 3 mL of aqueous methylamine 40 wt%, and the
     reaction stirred for 1 hour. The contents were
     concentrated and the residue was partitioned between
15   ethyl acetate (100 mL) and water (100 mL). The organic
     layer was dried over magnesium sulfate, filtered and
     concentrated to yield the crude product, which was
     purified by recrystallization from ethyl acetate heptane;
     (M+H)575, HRes.found 575.3267.

20

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Example 12F

5   Preparation of Pentanamide, 2S-[[(dimethylamino)acetyl]
amino]-N-[2R-hydroxy-3-[(3-methylpropyl)(4-
methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)
propyl]-3S-methyl-

10   Part A:

         To a solution of 2R-hydroxy-3-[(2-methylpropyl)
(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)
propylamine (1.70 g, 4.18 mmol) in 40 mL of
dichloromethane was added N-carbobenzyloxy-L-isoleucine-
15   N-hydroxysuccinamide ester (1.51 g, 4.18 mmol) and the
.solution stirred under nitrogen atmosphere for 16 hours.
The contents were concentrated in vacuo and the residue
was redissolved in ethyl acetate. The ethyl acetate
solution was washed with an aqueous solution of 5% KHSO$_4$,
20   saturated sodium bicarbonate, and saturated sodium
chloride, dried over magnesium sulfate, filtered, and
concentrated to yield 2.47g of crude product. The
product was purified by silica gel chromatography using 1
2:1 hexane:ethyl acetate eluant to yield 2.3 g. (84%
25   yield) of 2S-[(carbobenzyloxy)amino]-N-[2R-hydroxy-3-[(3-
methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-
(phenylmethyl)propyl]-3S-methylpentanamide.

     Part B:

30   (1.18 g, 1.8 mmol) of the product from Part A
. was dissolved in 50 mL of methanol, and to this was added
250 mg of 10% Palladium on Carbon while under a stream of

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nitrogen. The suspension was hydrogenated using 50 psig
of hydrogen for 20 hours. The contents were purged with
nitrogen and filtered through celite, and concentrated in
vacuo to yield 935 mg of 2S-(amino)-N-[2R-hydroxy-3-[(3-
5   methylpropyl)(4-methoxyphenylsulfonyl) amino]-1S-
(phenylmethyl)propyl]-3S-methylpentanamide, which was
used without further purification.

Part C:

10   (0.935 g, 1.8 mmol) of the amine from Part B
was dissolved in 15 mL of dioxane and to this was added
(190 mg, 1.85 mmol) of 4-methylmorpholine folowed by
(0.315 g, 1.8 mmol) of chloroacetic anhydride. The
reaction mixture was stirred under nitrogen atmosphere
15   for 3 hours, concentrated in vacuo, and redissolved in
ethyl acetate. The ethyl acetate solution was washed
with 50 mL of 5% aqueous KHSO4, saturated NaHCO3, and
saturated NaCl solution, dried over MgSO4, filtered and
concentrated to yield 613 mg, (68% yield) of 2S-
20   [(chloroacetyl)amino]-N-[2R-hydroxy-3-[(3-methylpropyi)
(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-
3S-methylpentanamide, after purification by silica gel
chromatography using 1:1 hexane:ethyl acetate.

25   Part D:

          To a solution of the chloroacetamide from Part
C (673 mg, 1.10 mmol) in 20 mL of tetrahydrofuran was
added 5 mL of 50 wt% aqueous dimethylamine and the
solution was stirred for 1 hour. The reaction was
30   concentrated and the residue was redissolved in 50 mL of
ethyl acetate and washed with 25 mL of water. The ethyl
acetate layer was dried over magnesium sulfate, filtered
and concentrated to yield a crude solid which was
purified by silica gel column chromatography using an
35   eluant of 97:3 dichloromethane:methanol to proivde 400 mg
of Pentanamide, 2S-[[dimethylamino)acetyl]amino]-N-[2R-
hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)
amino]-1S-(phenylmethyl)propyl]-3S-methyl-.

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Example 13A
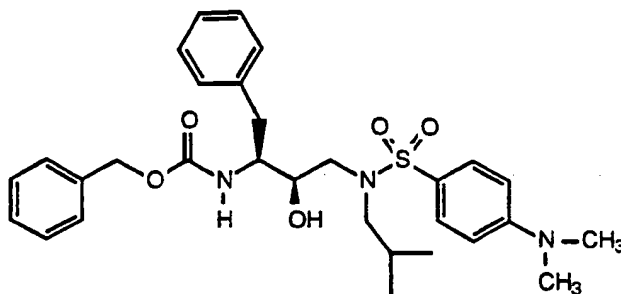
Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
dimethylaminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, phenylmethyl ester

      To a solution of 100mg (0.19 mmol) of carbamic
acid, [2R-hydroxy-3-[[(4-fluorophenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-,
phenylmethyl ester in 1 mL of pyridine was added 53 µL of
triethylamine and 120 µL (p.95 mmol) of 40% aqueous
dimethylamine. After heating for 24 hours at 100°C, the
solution was cooled, ethyl acetate added, then washed
with 5% citric acid, saturated sodium bicarbonate, dried
over magnesium sulfate, filtered and concentrated. The
resulting solid was recrystallized from ethyl
acetate/hexane to afford 10 mg of the desired product;
mass spectrum m/e = 540 (M+H).
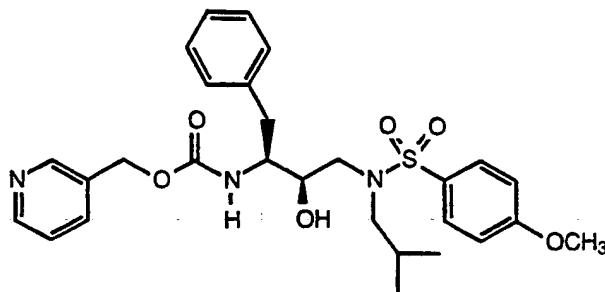
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Example 13B

5   Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
     methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
     (phenylmethyl)propyl]-, 3-pyridylmethyl ester

     Part A:

10   A solution of N-benzyloxycarbonyl-3S-amino-1,2-
     S-epoxy-4-phenylbutane (50g, 0.168 mol) and isobutylamine
     (246g, 3.24 mol) in 650 mL of isopropyl alcohol was
     refluxed for 1.25 hours. The solution was cooled to room
     temperature, concentrated in vacuo and then poured into
15   1L of stirring hexane whereupon the product crystallized
     from solution, was collected and air dried to give 57.6 g
     of N-[3S-benzyloxycarbonylamino-2R-hydroxy-4-phenyl]-N-
     isobutylamine, mp 108-109.5°C, mass spectrum
     m/e=371(M+H).

20

     Part B:

                The amine from part A (1.11g, 3.0 mmol) and
     triethylamine (324mg, 3.20 mmol) in 20 mL of methylene
     chloride was treated with 715 mg (3.46 mmol) of 4-
25   methoxybenzenesulfonyl chloride. The solution was
     stirred at room temperature for 6 hours, concentrated,
     dissolved in ethyl acetate, then washed with 1N potassium
     hydrogen sulfate, saturated sodium bicarbonate, brine,
     dried over magnesium sulfate, filtered and concentrated
30   to afford a clear oil. This was recrystallized from
     diethyl ether to afford 1.27 g of carbamic acid, [2R-
     hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)

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amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester, mp
97-101°C, mass spectrum m/e=541 (M+H).

Part C:

5   A solution of 930mg (3.20 mmol) of the product
of part B in 30 mL of methanol was hydrogenated in the
presence of 70 mg of a 10% palladium on carbon catalyst
under 40 psig for 17 hours, the catalyst was removed by
filtration, and the solution concentrated to afford 704
10   mg of [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propylamine, mass
spectrum m/e = 407 (M+H), which was used directly in the
next step without purification.

15   Part D:

          To a solution of 2.5g (22.9 mmol) of 3-
pyridylcarbinol in 100 mL of anhydrous acetonitrile was
added 8.8 g (34.4 mmol) of N,N'-disuccinimidyl carbonate
and 5.55 mL (68.7 mmol) of pyridine. The solution was
20   stirred for 1 hour and then concentrated in vacuo. The
residue was dissolved in ethyl acetate, then washed with
saturated sodium bicarbonate, brine, dried over magnesium
sulfate, filtered and concentrated to afford 5.3 g of N-
Hydroxysuccinimide-3-pyridylmethyl carbonate, mass
25   spectrum m/e = 251 (M+H), which was used directly in the
next step without purification.

Part E:

          To a solution of the amine from part C (2.87g,
30   7.0 mmol) and 1.38 mL of triethylamine in 24 mL of
anhydrous methylene chloride was added a solution of1.65g
(6.6 mmol) of N-hydroxysuccinimide-3-pyridyl carbonate
from part D in 24 mL of methylene chloride. The solution
was stirred for 1 hour, 100 mL of methylene chloride
35   added, then washed with saturated sodium bicarbonate,
brine, dried over sodium sulfate, filtered and
concentrated to afford 3.69 g of crude product.
Chromatography on silica gel using 2% methanol/methylene

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chloride to afford 3.27 g of carbamic acid, [2R-hydroxy-
3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-pyridylmethyl ester, mass
spectrum m/e = 548 (M+Li).

Example 13C

Preparation of Carbamic acid, [2R-hydroxy-3-
[(phenylsulfonyl)(2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-pyridylmethyl ester

Part A:

A solution of N-benzyloxycarbonyl-3S-amino-1,2-
S-epoxy-4-phenylbutane (50g, 0.168 mol) and isobutylamine
(246g, 3.24 mol) in 650 mL of isopropyl alcohol was
refluxed for 1.25 hours. The solution was cooled to room
temperature, concentrated in vacuo and then poured into
1L of stirring hexane whereupon the product crystallized
from solution, was collected and air dried to give 57.6 g
of N-[3S-benzyloxycarbonylamino-2R-hydroxy-4-phenyl]-N-
isobutylamine, mp 108-109.5 C, mass spectrum
m/e=371(M+H).

Part B:

The amine from part A (0.94g, 2.5 mmol) and
triethylamine (288 mg,2.85 mmol) in 20 mL of methylene
chloride was treated with 461 mg(2.61 mmol) of
benzenesulfonyl chloride. The solution was stirred at
room temperature for 16 hours, concentrated, dissolved
in ethyl acetate, then washed with 1N potassium hydrogen

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sulfate, saturated sodium bicarbonate, brine, dried over
magnesium sulfate, filtered and concentrated to afford a
clear oil. This was recrystallized from diethyl ether
and hexane to afford 0.73 g of carbamic acid, [2R-
5   hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, phenylmethyl ester, mp 95-99 C,
mass spectrum m/e=511 (M+H).

Part C:

10   A solution of 500mg of carbamic acid, [2R-
hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, phenylmethyl ester in 20 mL of
methanol was hydrogenated in the presence of 250 mg of a
10% palladium on carbon catalyst under 40 psig for 3
15   hours, the catalyst was removed by filtration, and the
solution concentrated to afford 352 mg of [2R-hydroxy-3-
[(phenylsulfonyl])2-methylpropyl)amino]-1S-
(phenylmethyl)propylamine, mass spectrum m/e = 377 (M+H),
which was used directly in the next step without
20   purification.

Part D:

         To a solution of 1.24 mmol of 5-norbornene-2,3-
dicarboximido carbonochloridate (Henklein, P., et. al.,
25   Synthesis 1987, 166-167) in 1 mL of anhydrous methylene
chloride, was added a solution of 43 µL (2.44 mmol) of 3-
pyridylcarbinol and 129 µL (1.6 mmol) of pyridine in 1 mL
of methylene chloride at 0°C under a nitrogen atmosphere.
After 4 hours at room temperature, 150 mg (0.4 mmol) of
30   [2R-hydroxy-3-[(phenylsulfonyl])2-methylpropyl)amino]-1S-
(phenylmethyl)propylamine from Part C above was added and
100 µL of pyridine. After stirring for 15 hours at room
temperature, ethyl acetate was added, then washed with 1N
hydrochloric acid, saturated sodium bicarbonate, brine,
35   dried over magnesium sulfate, filtered and concentrated
to afford 175 mg of crude product. Chromatography over
silica gel using 1% methanol/methylene chloride to afford
69 mg of pure carbamic acid, [2R-hydroxy-3-

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[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)
propyl]-, 3-pyridylmethyl ester, mass spectrum m/e =
512.2267 (M+H); calcd for C27H33N3O5S, 512.2219.

5   Example 13D
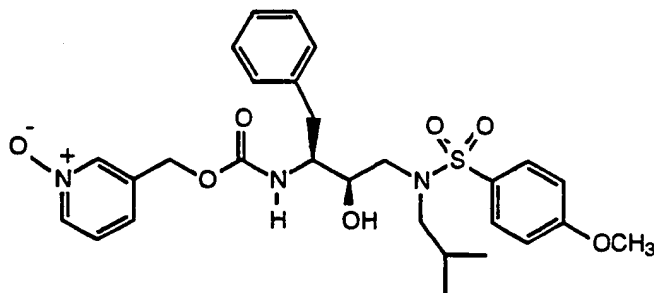
Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
10   methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
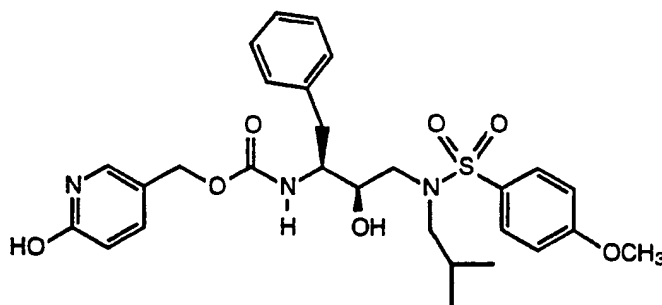   (phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide

        To a solution of 211mg (0.39 mmol) of carbamic
        acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
15   methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-
        pyridylmethyl ester in 5mL of methylene chloride at 0°C
        was added 500 mg of 50% 3-chloroperbenzoic acid. After
        stirring at room temperature for 1 hour, ethyl acetate
        was added, the solution washed with saturated sodium
20   bicarbonate, 0.2N ammonium hydroxide solution and brine,
        dried over magnesium sulfate, filtered and concentrated
        to afford 200 mg of crude product. This was
        chromatographed on C18 reverse phase material using 20-
        40% acetonitrile/water, then 100% acetonitrile to afford
25   90mg of the desired product, which was then
        recrystallized from ethyl acetate/isooctane to yield 34mg
        of pure carbamic acid, [2R-hydroxy-3-[[(4-
        methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
        (phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide;
30   mass spectrum m/e=564 (M+Li).
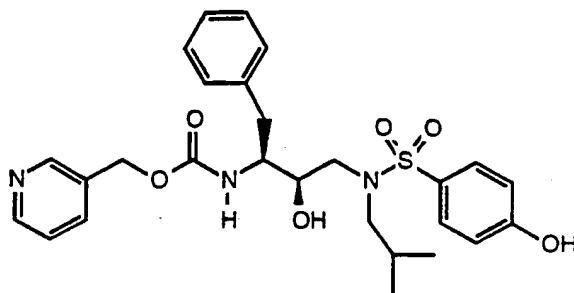
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Example 13E

Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester

Part A:

A solution of 0.98 g (1.85 mmol) of carbamic acid, [2R-hydroxy-3-[[(4-fluorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-phenylmethyl ester in 3.8 mL of anhydrous DMF was added to 22mg (7.4 mmol) of 80% sodium hydride in 2 mL of DMF. To this mixture was added 0.40g (3.7 mmol) of benzyl alcohol. After 2 hours, the solution was cooled to 0 C, water added, and then ethyl acetate. The organic layer was washed with 5% cirtic acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 0.90g of crude material. This was chromatographed on basic alumina using 3% methanol/methylene chloride to afford 0.70g of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine, cyclic carbamate; mass spectrum m/e=509(M+H).

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Part B:

        To a solution of 0.65g (1.28 mmol) of the
cyclic carbamate from part A in 15 mL of ethanol, was
added 2.6 mL (6.4 mmol) of 2.5N sodium hydroxide
5   solution. After 1 hour at reflux, 4 mL of water was
added and the solution refluxed for an additional eight
hours. The volatiles were removed, ethyl acetate added,
and washed with water, brine, dried over magnesium
sulfate, filtered and concentrated to afford 550 mg of
10 crude 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)
sulfonyl]amino-1S-(phenylmethyl)propylamine.

Part C:

        A solution of crude 2R-hydroxy-3-[(2-
15 methylpropyl)(4-benzyloxyphenyl)sulfonyl]amino-1S-
(phenylmethyl)propylamine in 10 mL of ethanol was
hydrogenated in the presence of 500 mg of a 10% palldium
on carbon catalyst under 50 psig of hydrogen for 2 hours.
The catalyst was removed by filtration and the solvent
20 removed in vacuo to afford 330 mg of 2R-hydroxy-3-[(2-
methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-
(phenylmethyl)propylamine, mass spectrum m/e = 393 (M+H).

Part D:

25   To a solution of 320 mg (0.82 mmol) of the
amine from part C in 6 mL of DMF, was added 192 mg (0.76
mmol) of N-hydroxysuccinimide-3-pyridylmethyl carbonate.
After 15 hours at room temperature, the DMF was removed in
vacuo, ethyl acetate added, washed with water, brine,
30 dried with magnesium sulfate, filtered and concentrated to
afford 390 mg of crude material. Chromatogrpahy on silica
gel using 50-80% ethyl acetate/hexane afforded 180 mg of
carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)
sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-,
35 3-pyridylmethyl ester, mass spectrum m/e = 528(M+H).
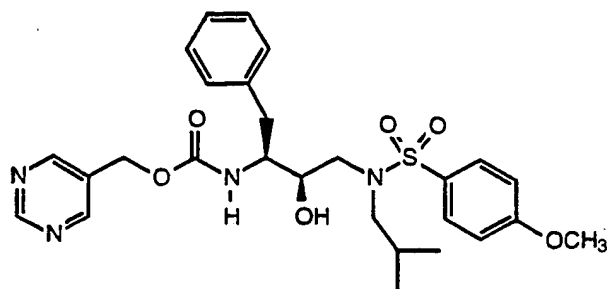
111

Example 13F

5   Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
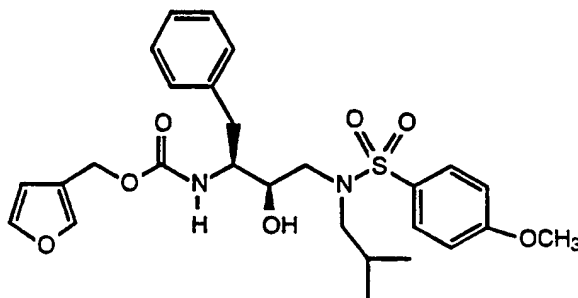(phenylmethyl)propyl]-, 5-pyrimidylmethyl ester

        To a solution of 9.5mg (0.09mmol) of 5-
10 pyrimidylcarbinol in 1mL of anhydrous acetonitrile at
    room temperature, was added 24mg (0.09mmol) of N,N'-
    disuccinimidyl carbonate and 19.1 µL (0.24mmol) of
    pyridine. After stirring for 5 hours, 32 mg (0.08mmol)
    of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)
15 sulfonyl]amino-1S-(phenylmethyl)propylamine was added and
    the solution stirred for 48 hours. After concentration
    in vacuo, methylene chloride was added, then washed with
    a 1:1 mixture of saturated sodium bicarbonate and brine,
    dried over magnesium sulfate, filtered and concentrated
20 to give 27 mg of crude product. Chromatography on silica
    gel using 2% methanol/methylene chloride afforded 22 mg
   of the desired product, mass spectrum m/e=543 (M+H).

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Example 13G
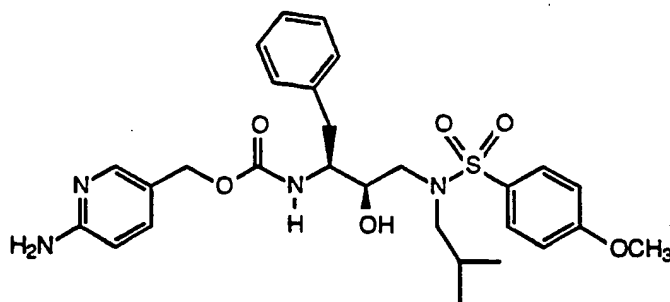
Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester.

Part A: Prepartion of Ethyl 6-Aminonicotinate

To a suspension of 1.3g (9.4 mmol) 6-aminonicotinic acid in 100 mL of ethanol, was bubbled in dry hydrochloric acid at 0°C, then the solution was refluxed until all the solids dissolved. The solvents were removed under reduced pressure, the residue dissolved in ethyl acetate, washed with saturated sodium bicarbonate, brine and concentrated to afford 1.37g of a white solid, m/e=166(M+H).

Part B: Preparation of Ethyl 6-(tert-Butyloxycarbonylamino)nicotinate

A mixture of 848 mg(5.1 mmol) of ethyl 6-aminonicotinate from part A, 1.11g(5.1 mmol) of di-tert-butylpyrocarbonate and 0.71 mL (5.1 mmol) of triethylamine in 10mL of anhydrous toluene was refluxed for 15 hours. The solution was cooled, ethyl acetate added, washed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 1.28g of the desired ethyl 6-(tert-butyloxycarbonylamino)nicotinate, m/e=267(M+H), which was used directly in the next step.

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Part C: Preparation of 6-(tert-Butyloxycarbonylamino)-3-
pyridylmethanol

5   To 4.6 mL (4.6 mmol) of a 1M solution of lithium aluminum
hydride in diethyl ether at -40°C under a nitrogen
atmosphere, was added a slution of 618mg (2.3 mmol) of ethyl
6-(tert-butyloxycarbonylamino)nicotinate from part B in 40
mL of anhydrous tetrahydrofuran. After the addition, this
was warmed to room temperature, stirred for 3 hours, cooled
10   to 0°C, and 145 μL of water, 145μL of 20% sodium hydroxide
solution and 290μL of water were successively added. To the
resulting mixture was added 50mL of tetrahydrofuran and
stirring continued for 30 minutes. Anhydrous magnesium
sulfate was added, the solids removed via filtration and the
15   filtrate concentrated under reduced pressure to afford 460
mg of the desired product, m/e=224(M+), which was used
directly in the next step.

Part D: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
20   methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-[(6-tert-
butyloxycarbonylamino)pyridyl]methyl ester

To a solution of 336 mg (1.5mmol) of 6-(tert-
25   butyloxycarbonylamino)-3-pyridylmethanol from part C in 14
mL of anhydrous acetonitrile at room temperature under a
nitrogen atmosphere, was added 384 mg(1.5mmol) of N,N'-
disuccinimidyl carbonate and 364 μL (4.5mmol) of anhydrous
pyridine. After 4 hours, 406mg (1mmol) of 2R-hydroxy-3-[(2-
30   methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-
(phenylmethyl)propylamine was added and stirring continued
for 19 hours. The solvent was removed under reduced
pressure, ethyl acetate added, washed with saturated sodium
bicarbonate, brine, dried over magnesium sulfate, filtered
35   and concentrated to afford 702 mg of crude product.
Chromatography on silica gel using 1% methanol/methylene
chloride as eluent afforded 170 mg of the desired carbamic
acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-

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methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-
butyloxycarbonylamino)pyridyl]methyl ester, m/e=663(M+Li).

Part E: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
5   methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester


To 5mL of 4N hydrochloric acid in dioxane at room
temperature, was added 150mg (0.23mmol) of carbamic acid,
10   [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-
butyloxycarbonylamino)pyridyl]methyl ester from part D.
After stirring at room temperature for 28 hours, the solvent
was removed under reduced pressure, the resulting solids
15   triturated with diethyl ether, then dissolved in ethyl
acetate and saturated sodium bicarbonate slution, separated,
the organic layer washed with brine, dried with magnesium
sulfate, filtered and concentrated. The residue was
chromatographed on silica gel using 2.5% methanol/methylene
20   chloride to yield 59mg of the desired carbamic acid, [2R-
hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)
amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl
ester, m/e=557(M+H).
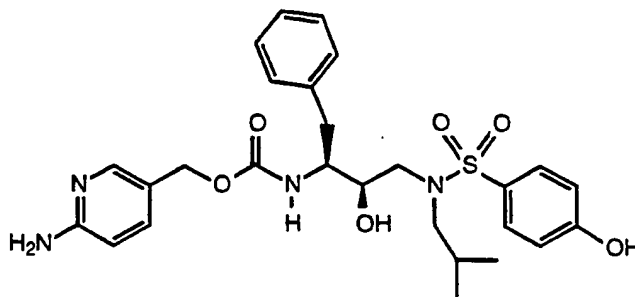
115

Example 13H

5   Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
     hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
     (phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester.

     Part A: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
10   methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
     (phenylmethyl)propyl]-, 3-[(6-tert-
     butyloxycarbonylamino)pyridyl]methyl ester

     To a solution of 505 mg (2.25mmol) of 6-(tert-
15   butyloxycarbonylamino)-3-pyridylmethanol from in 20 mL of
     anhydrous acetonitrile at room temperature under a nitrogen
     atmosphere, was added 576 mg (2.25mmol) of N,N'-
     disuccinimidyl carbonate and 546 μL (6.75mmol) of anhydrous
     pyridine. After 1 hour, 837mg (1.87mmol) of 2R-hydroxy-3-
20   [(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-
     (phenylmethyl)propylamine was added and stirring continued
     for 3 hours. The solvent was removed under reduced
     pressure, ethyl acetate added, washed with saturated sodium
     bicarbonate, brine, dried over magnesium sulfate, filtered
25   and concentrated to afford 1.37g of crude product.
     Chromatography on silica gel using 1% methanol/methylene
     chloride as eluent afforded 830 mg of material which was
     identified as a mixture of the desired carbamic acid, [2R-
     hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)
30   amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-
     butyloxycarbonylamino)pyridyl]methyl ester and the cyclic
     carbamate derived from the 2R-hydroxy-3-[(2-methylpropyl)(4-

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hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine.
The mixture was very difficult to separate, so was used as
is in the next step.

5   Part B: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
     hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
     (phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester

     To 830mg of the mixture from part A, was added 50mL of a 1:1
10   mixture of trifluoroacetic acid and methylene chloride.
     After 2.5 hours at room temperature, the solvent was removed
     under reduced pressure, ethyl acetate added, washed with
     saturated sodium bicarbonate, dried over magnesium sulfate,
     filtered and concentrated to afford 720 mg of crude
15   material. This was chromatgraphed on silica gel using 5%
     methanol/ethyl acetate as eluent to yield 220mg of product,
     which was recrystallized from methylene chloride/diethyl
     ether to afford 108mg of the desired carbamic acid, [2R-
     hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)
20   amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl
     ester, m/e=549(M+Li).

Example 131

25.

Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-(6-hydroxypyridyl)methyl ester.

30

     Part A: Preparation of tert-Butyldimethylsilyl 6-(tert-
     butyldimethylsiloxy)nicotinate

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To a solution of 5.0g (35.9mmol) of 6-hydroxynicotinic acid
in 200mL of anhydrous N,N-dimethylformamide at room
temperature, was added 8.56g (125mmol) of imidazole and then
5   13.5g (89mmol) of tert-butyldimethylsilyl chloride. After
20 hours, the solvent was removed under reduced pressure,
ethyl acetate added, washed with water, 5% citric acid,
saturated sodium bicarbonate, brine, dried over anhydrous
magnesium sulfate, filtered and concentrated to afford 10.5
10   g of crude material, m/e=368(M+H).

Part B: Preparation of 3-(6-tert-butyldimethylsiloxy)
pyridylcarbinol

15   To 11mL of 1M solution of lithium aluminum hydride in
diethyl ether at -35°C under a nitrogen atmosphere, was
added a solution of 2.0g (5.46mmol) of product from part A
in 20mL of anhydrous diethyl ether. After 30 minutes, the
reaction was warmed to 0°C and stirred for 40 minutes. The
20   solution was then quenched by the careful addition of 0.42mL
of water, 0.42mL of 20% sodium hydroxide solution, and
0.84mL of ater. Ethyl acetate was added, the precipate
filtered and the organic phase concentrated to yield 0.93 g
of crude 3-(6-tert-butyldimethylsiloxy)pyridylcarbinol,
25   which was used directly in the next step.

Part C: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-(6-hydroxypyridyl)methyl ester
30
To a solution of 860mg (3.6mmol) of material from part B in
15mL of anhydrous acetonitrile, was added 919mg (3.6mmol) of
N,N'-disuccinimidyl carbonate and 0.87mL of pyridine. After
1 hour, 1.42g(3.5mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-
35   methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
was added. After 14 hours at room temperature, the solvent
was removed under reduced pressure, the residue disslved in
ethyl acetate, washed with 5% citric acid, saturated sodium

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bicarbonate, brine, dried over magnesium sukfate, filtered
and concentrated to afford 2.1 g of crude material. This
was directly deprotected by dissolving in 40mL of 80% acetic
acid/water and stirring for 2 hours. The solvents were
5   removed under reduced pressure, the residue dissolved in
ethyl acetate, washed with saturated sodium bicarbonate,
brine, dried over magnesium sulfate, filtered and
concentrated to afford 1.7g of crude product. This was
chromatographed on silica gel using 50-100% ethyl
10   acetate/hexane to provide a fraction of 0.19g of fairly pure
material, which was further purified by reverse phase
chromatography using 15-40% acetonitrile/water (0.05%
trifluoroacetic acid) to provide 120mg of the desired
carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-
15   methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-
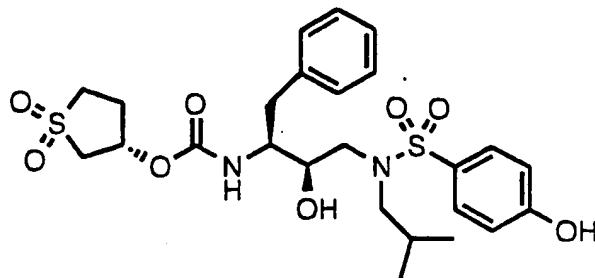hydroxypyridyl)methyl ester, m/e=558(M+H).

Example 13J
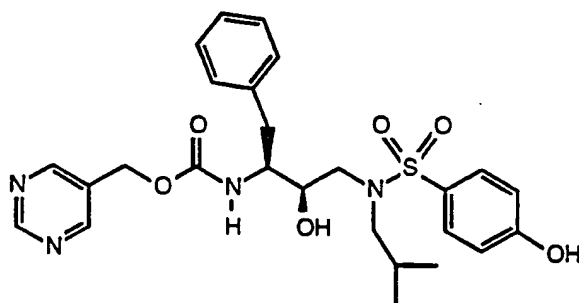
20

Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl], 5-pyrimidylmethyl ester.

25

To a solution of 237mg (2.15mmol) of 5-pyrimidylcarbinol
in 24mL of anhydrous acetonitrile , was added 602mg
(2.35mmol) of N,N'-disuccinimidyl carbonate and then
0.47mL of pyridine. After stirring for 4.5 hours, 766mg
30   (1.96mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-
hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
was added. After stirring for 19 hours, the solvent was

removed under reduced pressure, ethyl acetate added,
washed with 5% citric acid, saturated sodium bicarbonate,
brine, dried over anhydrous magnesium sulfate, filtered
and concentrated to afford 1.0 g of crude material.

5   Chromatography on silica gel using 50-100% ethyl
acetate/hexane as eluent afforded 450 mg of the desired
carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)
sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-,
5-pyrimidylmethyl ester, m/e=529(M+H).

10

<u>Example 13K</u>

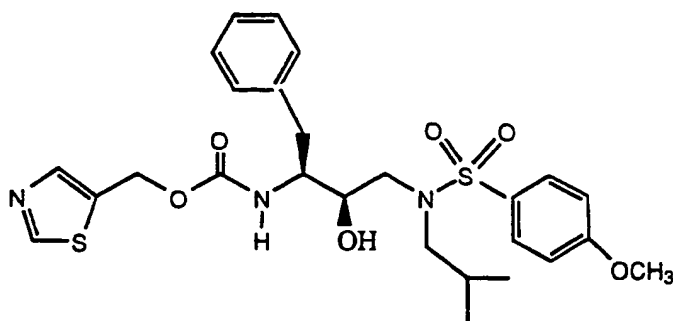15   <u>Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, 3-furanylmethyl ester</u>

To a solution of 98mg (1 mmol) of 3-(hydroxymethyl)furan
20   in 3 mL of anhydrous acetonitrile, was added 242 µL of
pyridine and then 256 mg of N,N'-disuccinimidyl carbonate
at room temperature under nitrogen. After 45 minutes,
406 mg (1 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-
methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
25   was added. After stirring at room temperature for 16
hours, ethyl acetate was added, washed with 5% citric
acid, saturated sodium bicarbonate and brine, dried over
magnesium sulfate, filtered and concentrated to afford
565 mg of crude product. This was chromatographed on
30   silica gel using 50% ethyl acetate/hexane as eluent to
afford 305mg of a white foam, which was recrystallized
from diethyl ether/hexane to yield 245 mg of pure

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carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl]
(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-
furanylmethyl ester, m/e = 537(M+Li).

5

Example 14
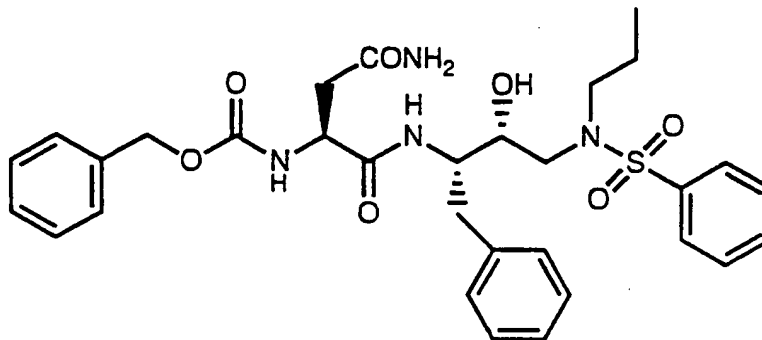
10 Preparation of phenylmethyl[3-amino-1S-[[2R-hydroxy-3-
    [(3-propyl)(phenylsulfonyl)amino]-1S-
    (phenylmethyl)amino]-carbonyl]-3-oxopropyl]carbamate

Phenylmethyl [2R-hydroxy-3-[(3-propyl)(phenylsulfonyl)
15 amino]-1S-(phenylmethyl)propyl]carbamate (200 mg, 0.40
mmol) was deprotected by hydrogenation over 10% palladium
on carbon and the resulting free amine was coupled with
N-CBZ-L-asparagine (157 mg,0.42 mmol) in the presence of
N-hydroxybenzotriazole (114 mg, 0.84 mmol) and EDC
20 (130 mg, 0.67 mmol) to give phenylmethyl[3-amino-1S-[[2R-
hydroxy-3-[(3-propyl)(phenylsulfonyl)amino]-1S-
(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate as a
solid. Anal. Calcd for $C_{31}H_{38}N_4O_7S \cdot 0.2H_2O$: C,60.61;
H,6.30; N,9.12. Found: C,60.27; H,6.16; N,8.93.

25

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Example 15A
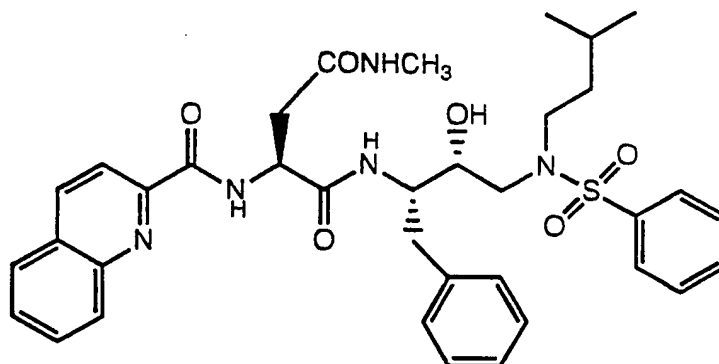
5   Preparation of N¹-[2R-hydroxy-3-[(3-methylbutyl)(phenyl-
sulfonyl)amino]-N⁴-methyl-1S-(phenylmethyl)propyl]-2S-
[(2-quinolinylcarbonyl)amino]butanediamide

Part A:

10   N²-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-
asparagine was prepared from Boc-L-aspartic acid alpha-
benzyl ester (1.0 g, 3.09mmol), methylamine.HCl (209 mg,
3.09mmol), EDC (711 mg, 3.7 mmol), 1-hydroxybenzotriazole
(627 mg, 4.63 mmol), and N-methylmorpholine (0.7 mL, 6.3
15 mmol), in DMF (20mL). After stirring overnight at room
temperature, the reaction mixture was diluted with ethyl
acetate, washed with water, saturated sodium bicarbonate,
5% citric acid, brine, dried over magnesium sulfate and
concentrated to an oil. The oil was taken up in 20 mL
20 dry ethanol, and hydrogenated in the presence of 10% w/w
of 10% Pd on C at atmospheric pressure and room
temperature overnight. The mixture was filtered through
Celite and concentrated to a white solid foam, 670 mg.

25 Part B:

          A solution of phenylmethyl [2R-hydroxy-3-[(3-
methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)-
propyl]carbamate (310 mg, 0.59 mmol) in methanol (10mL)
was hydrogenated over 10% palladium on carbon for 3 h.,
30 filtered through diatomaceous earth and concentrated to

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give the product as an oil (214 mg). This free amine
(208 mg, 0.53 mmol) was coupled with N2-[(1,1-
dimethylethoxy)-carbonyl]-N-methyl-L-asparagine (137 mg,
0.56 mmol) in the presence of N-hydroxybenzotriazole (102

5   mg, 0.76mmol) and EDC (130 mg, 0.67mmol) to yield 290 mg
of N1[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)-
amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-[(1,1-
dimethylethoxy-carbonyl)amino]butane diamide.

10   Part C:

N^1[2R-hydroxy-3-[(3-methylbutyl)(phenyl-
sulfonyl)amino]-N^4-methyl-1S-(phenylmethyl)propyl]-2S-
[(1,1-dimethylethoxycarbonyl)-amino]butane diamide (270
mg, 0.43 mmol) was stirred in 4N HCl in dioxane (5 mL) at

15   room temperature for 0.5 hr. Solvent and excess reagent
were evaporated to dryness. The product was dried in
vacuo. This material (125 mg, 0.225 mmol) was then
reacted with 2-quinolinecarboxylic acid
N-hydroxysuccimide ester (61 mg, 0.225 mmol),

20   N-methylmorpholine (50 uL, 0.45 mmol) in methylene
chloride (2 mL) for 3 h. The product N^1[2R-hydroxy-3-
[(3-methylbutyl)(phenylsulfonyl)amino]-N^4-methyl-1S-
(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)-
amino]butanediamide was purified by silica gel

25   chromatography. Anal. Calcd for $C_{36}H_{43}N_5O_6S \cdot 0.2H_2O$:
C,63.83; H,6.45; N,10.34. Found: C,63.64; H,6.40;
N,10.34.

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Example 15B
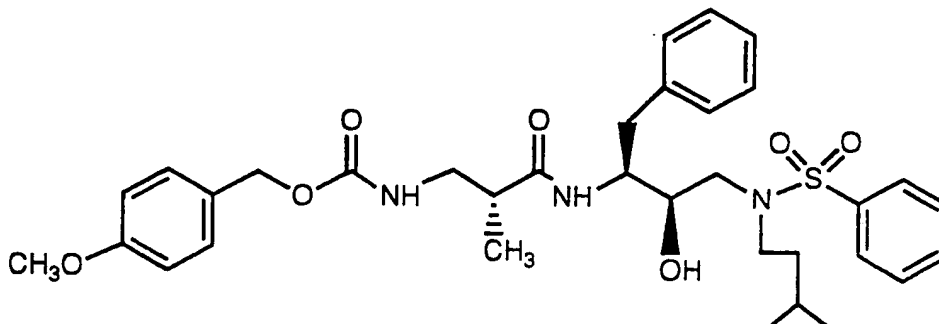
5   Preparation of Carbamic acid, [3-[[2-hydroxy-3-[(3-
     methylbutyl)(phenylsufonyl)amino]-1-
     (phenylmethyl)propyl]amino]-2-methyl-3-oxopropyl]-, (4-
     methoxyphenyl)methyl ester, [1S-[1R*(S*),2S*]]-

10   Carbamic acid, [2R-hydroxy-3-[(3-methylbutyl)
     (phenylsulphonyl)amino]-1S-(phenylmethyl)propyl]-,
     phenylmethyl ester (4.10g, 7.8 mmol) was hydrogenated in
     a solution of methanol and ethanol using catalytic Pd/C
     10% at 50 psig hydrogen for 3 hours. The catalyst was
15   filtered and the solvents removed in vacuo to yield 3.0
     grams of free amine. In a separate flask, 2.09g, (7.8
     mmol), of N-Moz-AMBA was added to 10 mL of
     dimethylformamide and 1.58g, (1.5 equiv.), of N-
     hydroxybenzoltriazole and the solution was cooled to 5°C.
20   To this solution was added 1.49g, (7.8 mmol), of EDC and
     the solution stirred for 30 min. To this was added the
     free amine in 10 mL of dimethylformamide, and the
     reaction was stirred for 20 hours. The solvent was
     removed by evaporation and the crude material was
25   partitioned between ethyl acetate and saturated aqueous
     sodium bicarbonate. The ethyl acetate layer was washed
     with 5% potassium hydrogen sulfate and brine, dried over
     magnesium sulfate, filtered and concentrated to yield
     2.58 grams (52%) of pure product after recrystallization
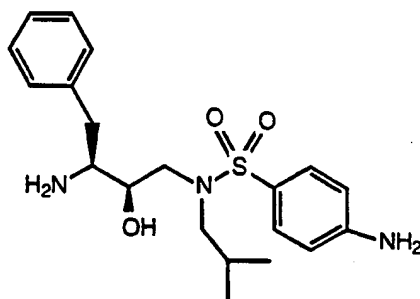30   from ethyl acetate, ether, and hexanes.

124

Example 16A
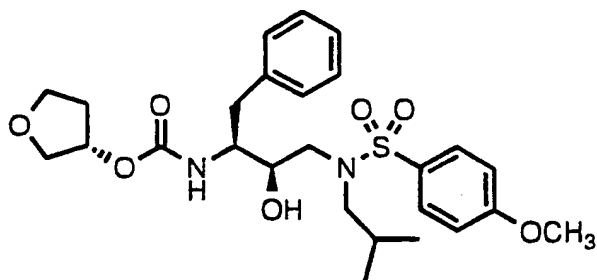
5   Preparation of Carbamic acid. [2R-hydroxy-3-[(4-
      methoxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
      (phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester,

      To a solution of 406 mg (1.0 mmol) of [2R-hydroxy-3-[[(4-
10   methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
      (phenylmethyl)propylamine in 5.0 mL of dichloromethane
      containing 150 mg (1.5mmol) of triethylamine was added
      280mg (1.22 mmol) of N-succinimidyl-3S-tetrahydrofuranyl
      carbonate and the reacton mixture was stirred for 2
15   hours, an additonal 136 mg (0.3mmol) of amine was added
      to the mixture and the solution stirred another 2 hours.
      The contents were diluted with 50 mL of ethyl acetate and
      washed with 5% aqueous citric acid, saturated sodium
      bicarbonate, and brine, then dried over magnesium
20   sulfate, filtered and concentrated to yield 330 mg of
      crude product. Purification by silica gel chromatography
      using an eluant of 1:1 to 2:1 ethyl acetate/hexanes
      gradient provided Carbamic acid, [2R-hydroxy-3-[(4-
      methoxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
25   (phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester as a
      white solid. m/z = 521 (M+H) calc. 521.2311 obs.
      521.2311.

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Example 16B

5   Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
     hydroxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
     (phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester.
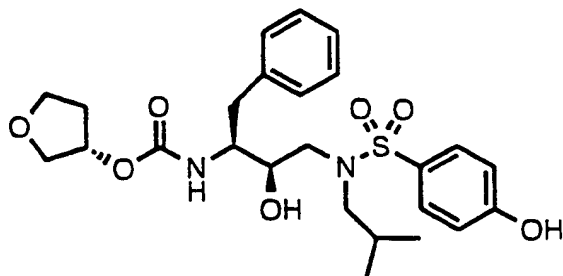
To a solution of 435 mg (1.0 mmol) of [2R-hydroxy-3-[[(4-
10   hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
     (phenylmethyl)propylamine in 3.0 mL of dimethylformamide
     was added 225mg (0.98 mmol) of N-succinimidyl-3S-
     tetrahydrofuranylcarbonate and the solution was stirred
     overnight. The mixture was diluted with 50 mL of ethyl
15   acetate and washed with 5% aqueous citric acid,
     saturated sodium bicarbonate, and brine, dried over
     magnesium sulfate, filtered and concentrated to yield 515
     mg of crude product. Purificaton by silica gel
     chromatography using and eluant of 1:1 ethyl acetate:
20   hexanes provided 315 mg of Carbamic acid, [2R-hydroxy-3-
     [(4-hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-
     (phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester, as a
   white solid. HRMS calc. 507.2165, obs. 507.2155.
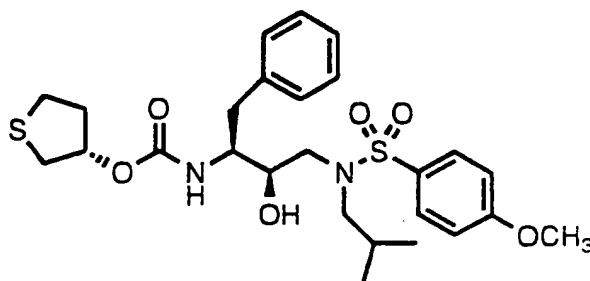
126

Example 16C

5   Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
     methoxyphenylsulfonyl)(2-methylpropyl)amino]-1S-
     (phenylmethyl)propyl-, tetrahydrothiophen-3S-yl ester.

To a solution of 215 mg (2.0mmol) of 3S-hydroxythiophene,
10   415 μL of anhydrous pyridine,and 2 mL of dry acetonitrile
     was added 512 mg (2.0 mmol) of N,N'-Dimethylsuccinimidyl
     carbonate and this suspension was stirred for 45 minutes.
     To this clear solution was added a solution of 700 mg
     (1.7 mmol) of [2R-hydroxy- 3-[[(4-methoxyyphenyl)
15   sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)
     propylamine in 2.0 mL of acetonitrile and stirred for 12
     hours. The contents were concentrated, and the residue
     was partitioned between ethyl acetate and 5% aqueous
     potassium hydrogen sulfate. The organic layer was washed
20   with saturated sodium bicarbonate and then brine, dried
     over sodium sulfate, filtered and concentrated to yield
     780 mg of crude material. Purificaton by silica gel
     chromatograpy using an eluant of 10:10:1 ethyl acetate:
     hexane:methanol provided 520 mg of Carbamic acid, [2R-
25   hydroxy-3-[(4-methoxyphenylsulfonyl)(2-methylpropyl)
     amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-
     yl-ester, as a crystalline white solid. m.p.= 162-3°C,
     m/z= 553 (M+H).

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Example 16D
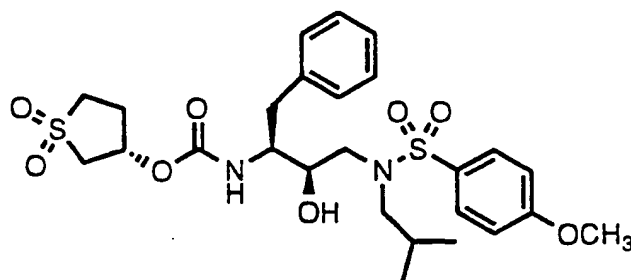
5   Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
     methoxyphenylsulfonyl) (2-methylpropyl)amino]-1S-
     (phenylmethyl)propyl-, 1,1-dioxotetrahydrothiophen-3S-yl
     ester

10   To a solution of 270 mg (0.5 mmol) of Carbamic acid,
     [2R-hydroxy-3-[(4-methoxyphenylsulfonyl) (2-methylpropyl)
     amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl
     ester in 30 mL of dichloromethane was added 400 mg (1.2
     mmol) of m-chloroperbenzoic acid (50 wt%) and the mixture
15   was stirred for 12 hours. The contents were diluted with
     10 mL of 10% aqueous sodium metabisulfite and stirred for
     30 minutes. The organic layer was washed with saturated
     sodium bicarbonate, dried over sodium sulfate, filtered
     and concentrated to yield 290 mg of crude product.
20   Purification by silica gel chromatography using an eluant
     of 10:10:1 ethyl acetate:hexane:methanol provided 260 mg
     of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl
     sulfonyl) (2-methylpropyl)amino]-1S-(phenylmethyl)propyl-,
     1,1-dioxotetrahydrothiophen-3S-yl ester, as a white
25   crystalline solid. m.p.= 69 ° C, m/z = 569 (M+H).
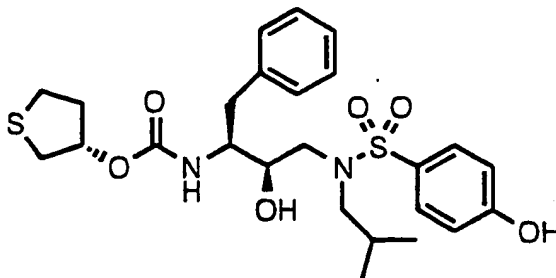
128

Example 16E

5   Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl ester,

To a solution of 125 mg (1.2 mmol) of 3-S-
10   hydroxythiophene, 250 μL of anhydrous pyridine, and 1 mL
of dry acetonitrile was added 307 mg (1.2 mmol) of N,N'-
dimethylsuccinimidyl carbonate and this suspension was
stirred for 45 minutes. To this clear solution was added
a solution of 445 mg (1.0 mmol) [2R-hydroxy-3-[[(4-
15   hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propylamine in 1.0 mL of acetonitrile and
stirred for 12 hours. The contents were concentrated,
and the residue was partitioned between ethyl acetate and
5% aqueous potassium hydrogen sulfate. The organic layer
20   was washed with saturated sodium bicarbonate and then
brine, dried over sodium sulfate, filtered and
concentrated to yield 460 mg of crude material.
Purificaton by silica gel chromatograpy using an eluant
of 10:10:1 ethyl acetate: hexane:methanol provided 235 mg
25   of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl
sulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-,
tetrahydrothiophen-3S-yl ester, as a crystalline white
solid. m.p.= 184-85°C , m/z = 529 (M+Li).

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Example 16F

5   Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
    hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-
    (phenylmethyl)propyl-, 1,1-dioxotetrahydrothiophen-3S-yl
    ester

10   To a solution of 125 mg (0.24 mmol) of carbamic acid,
     [2R-hydroxy-3-[(4-hydroxyphenylsulfonyl)(2-methylpropyl)
     amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl
     ester in 30 mL of dichloromethane was added 240 mg (0.7
     mmol) of m-chloroperbenzoic acid (50 wt%) and the mixture
15   was stirred for 12 hours. The contents were diluted with
     5 mL of 10% aqueous sodium metabisulfite and stirred for
     30 minutes. The organic layer was washed with saturated
     sodium bicarbonate, dried over sodium sulfate, filtered
     and concentrated to yield 110 mg of crude product.
20   Purification by silica gel chromatography using an eluant
     of 1:1 to 2:1 ethyl acetate:hexane:methanol provided 100
     mg of carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl
     sulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-,
     1,1-dioxotetrahydrothiophen-3S-yl-ester, as a white
25   crystalline solid, m.p.= 190°C, m/z= 561 (M+Li).

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Example 17A

5   Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
     methoxyphenyl)sulfonyl](methylpropyl)amino]-1S-
     (phenylmethyl)propyl]-, 5-thiazolylmethyl ester

     Part A: Preparation of Methyl 2-aminothiazole-5-
10   carboxylate

     Methyl chloroacetate 190 g (1.75 mol) and methyl formate
     111 g (1.80 mol), were added dropwise to a suspension of
     100 g (1.8 moL) of sodium methoxide in 450 mL of dry
15   toluene at 5°C over 2 hours. After an additional 2.5
     hours at 0°C. The contents were diluted with 600 mL of
     water and the layers separated. The aqueous phase was
     acidified with 113 mL of concentrated hydrochloric acid.
     The aqueous solution was placed in a 2 liter flask and
20   175 grams of thiourea was added and to solution was
     heated to reflux for 1.45 hours. To the cooled solution
     was added 25 g of DARCO activated charcoal and filtered
     through filter paper. The crude dark yellow solution was
     neutralized with 2.5 N sodium hydroxide upon which time
25   an amber solid precipitated which was filtered and air
     dried to yield 147 g of desired methyl 2-aminothiazole-5-
     carboxylate. m/e = 159(M+H).

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Part B: Preparation of Methyl 5-thiazolecarboxylate

To a solution of 35 mL (30.5 g, 260 mmol) of isoamyl
nitrite in 120 mL of dioxane at 80°C under nitrogen, was
5   slowly added a slurry of 20.0 g (126 mmol) of methyl 2-
amino-5-thiazolecarboxylate over a 45 minute period.
After refluxing for a further 1 hour, the solution was
cooled, concentrated, dissolved in ethyl acetate, washed
with saturated sodium bicarbonate, brine, dried over
10   magnesium sulfate, filtered and concentrated to afford 28
g of the crude product. This was chromatographed on 400
g of silica gel using 20% ethyl acetate/hexane to afford
9.07 g of purified material, which was crystallized from
methylene chloride/hexane to yield 7.64g of pure methyl
15   5-thiazolylcarboxylate, m/e=144(M+H).

Part C: Preparation of 5-thiazolemethanol

To a solution of 11.73 g (82 mmol) of methyl 5-
20   thiazolylcarboxylate in 105 mL of anhydrous
tetrahydrofuran at 0°C under nitrogen, was added 90 mL
(90 mmol) of a 1.0M lithium aluminum hydride solution in
diethyl ether over a 35 minute period. After stiiring at
room temperature for 30 minutes, the solution was cooled
25   to 0°C, and carefully quenched by the addition of 3 mL of
water, 3 mL of 20% sodium hydroxide solution, and 6 mL of
water, then 100mL of tetrahydrofuran was added. After
stirring for 1 hour, the mixture was filtered, the solid
was washed with tetrahydrofuran, and the filtrate
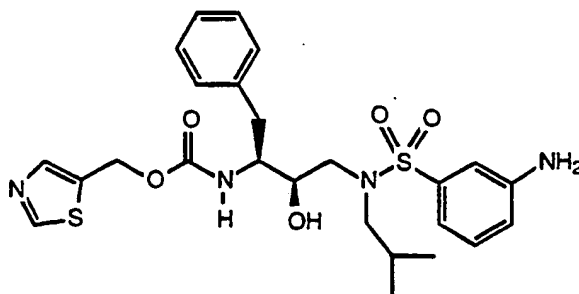30   concentrated to afford 7.56 g of 5-thiazolylmethanol.

Part D: Preparation of Carbamic acid, [2R-hydroxy-3-
[[(4-methoxyphenyl)sulfonyl](methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 5-(thiazolyl)methyl ester
35

To a solution of 115 mg (1.00 mmol) of 5-(hydroxymethyl)
thiazole in 3 mL of anhydrous acetonitrile, was added 0.25
mL (0.25 g, 3.09 mmol) of pyridine and then 256 mg (1.03

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mmol) of N,N'-disuccinimidyl carbonate at room temperature
under nitrogen. After 45 minutes, 406 mg (1.00 mmol) of 2R-
hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-
1S-(phenylmethyl)propylamine was added. After stirring at
5   room temperature for 15 hours, ethyl acetate was added,
washed with water, saturated sodium bicarbonate and brine,
dried over magnesium sulfate, filtered and concentrated to
afford 500mg of crude product. This was chromatographed on
silica gel using 80% ethyl acetate/hexane as eluent to
10   afford 307 mg of a white solid, which was identified as the
desired carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)
sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-
thiazolylmethyl ester, m/e = 548(M+H).

15   Example 17B

Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
20   hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, 5-thiazolylmethyl ester

To a solution of 115 mg (1.00 mmol) of 5-(hydroxymethyl)
thiazole in 3 mL of anhydrous acetonitrile, was added 0.25
25   mL (0.25 g, 3.09 mmol) of pyridine and then 256 mg (1.03
mmol) of N,N'-disuccinimidyl carbonate at room temperature
under nitrogen. After 45 minutes, 392 mg (1.00 mmol) of 2R-
hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-
1S-(phenylmethyl)propylamine was added. After stirring at
30   room temperature for 15 hours, ethyl acetate was added,
washed with water, saturated sodium bicarbonate and brine,

dried over magnesium sulfate, filtered and concentrated to
afford 450 mg of crude product. This was chromatographed on
silica gel using 80% ethyl acetate/hexane as eluent to
afford 270 mg of a white solid, which was identified as the
5   desired carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)
sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-
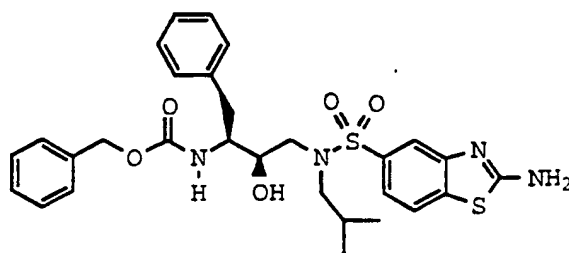thiazolylmethyl ester, m/e =534 (M+H).

Example 18A

10

Preparation of 2R-hydroxy-3-[[(4-aminophenyl)sulfonyl] (2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

15

Part A: Preparation of Carbamic acid, 2R-hydroxy-3-[[(4-
nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, phenylmethyl ester

20 To a solution of 4.0 g (10.8 mmol) of N-[3S-benzyloxy
carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in
50mL of anhydrous methylene chloride, was added 4.5mL
(3.27g, 32.4 mmol) of triethylamine. The solution was
cooled to 0°C and 2.63g (11.9 mmol) of 4-nitrobenzene
25 sulfonyl chloride was added, stirred for 30 minutes at
0°C, then for 1 hour at room temperature. Ethyl acetate
was added, washed with 5% citric acid, saturated sodium
bicarbonate, brine, dried and concentrated to yield 5.9 g
of crude material. This was recrystallized from ethyl
30 acetate/hexane to afford 4.7 g of pure carbamic acid,
[2R-hydroxy-3-[[(4-nitrophenyl)sulfonyl](2-methylpropyl)

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amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester,
m/e=556(M+H).

Part B: Preparation of 2R-hydroxy-3-[[(4-aminophenyl)
5   sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)
propylamine

A solution of 3.0g (5.4 mmol) of carbamic acid, 2R-
hydroxy-3-[[(4-nitrophenyl)sulfonyl](2-methylpropyl)
10   amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 20
mL of ethyl acetate was hydrogenated over 1.5 g of 10%
palladium-on-carbon catalyst under 35 psig of hydrogen
for 3.5 hours. The catalyst was removed by filtration
and the solution concentrated to afford 2.05 g of the
15   desired 2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propylamine,
m/e=392(M+H).

Example 18B

20
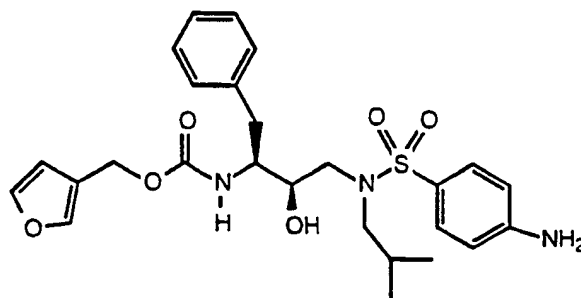
Preparation of Carbamic acid, 2R-hydroxy-3-[[(4-
aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
25   (phenylmethyl)propyl-, 3-furanylmethyl ester

To a solution of 104mg (1.06 mmol) of 3-(hydroxymethyl)
furan in 2 mL of anhydrous acetonitrile, was added 0.26
mL (0.25g, 3.18 mmol) of pyridine and then 277 mg (1.06
30   mmol) of N,N'-disuccinimidyl carbonate at room
temperature under nitrogen. After 45 minutes, 415 mg
(1.06 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-

aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
was added. After stirring at room temperature for 72
hours, ethyl acetate was added, washed with 5% citric
acid, saturated sodium bicarbonate and brine, dried over
5   magnesium sulfate, filtered and concentrated to afford
550 mg of crude product. This was chromatographed on
silica gel using 50% ethyl acetate/hexane as eluent to
afford 230 mg of a white foam, which was identified as
the desired carbamic acid, 2R-hydroxy-3-[[(4-
10   aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, 3-furanylmethyl ester, m/e = 522
(M+Li).

<u>Example 18C</u>
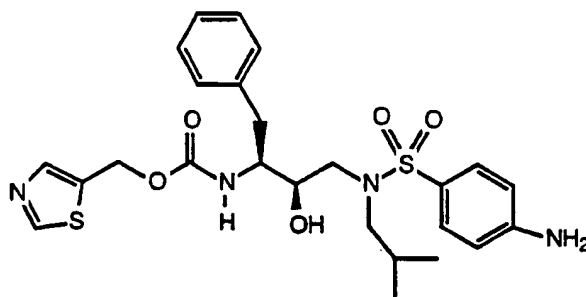
15

<u>Preparation of Carbamic acid, 2R-hydroxy-3-[[(4-</u>
<u>aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-</u>
20   <u>(phenylmethyl)propyl-, 5-thiazolylmethyl ester</u>

To a solution of 118mg (1.03 mmol) of 5-(hydroxymethyl)
thiazole in 3 mL of anhydrous acetonitrile, was added
0.25 mL (0.24g, 3.09 mmol) of pyridine and then 264 mg
25   (1.03 mmol) of N,N'-disuccinimidyl carbonate at room
temperature under nitrogen. After 45 minutes, 403 mg
(1.03 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-
aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
was added. After stirring at room temperature for 15
30   hours, ethyl acetate was added, washed with 5% citric
acid, saturated sodium bicarbonate and brine, dried over
magnesium sulfate, filtered and concentrated to afford

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350 mg of crude product. This was chromatographed on
silica gel using 80% ethyl acetate/hexane as eluent to
afford 290 mg of a white solid, which was identified as
the desired carbamic acid, 2R-hydroxy-3-[[(4-
5   aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, 5-thiazolylmethyl ester, m/e = 539
(M+Li).

<u>Example 18D</u>
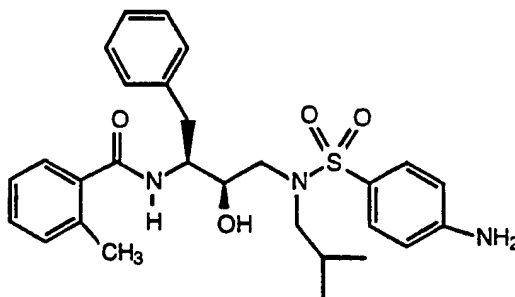
10

<u>Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-
aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
15   (phenylmethyl)propyl]-2-methyl</u>

To a solution of 391 mg (1 mmol) of 2R-hydroxy-3-[(2-
methylpropyl)(4-aminophenyl)sulfonyl]amino-1S-
(phenylmethyl)propylamine in 3 mL of anhydrous methylene
20   chloride, was added 0.42 mL (3 mmol) of triethylamine,
then at room temperature, 0.12 mL (0.9 mmol) of ortho-
toluoyl chloride was added. After 15 hours at room temp
ethyl acetate was added, washed with 5% citric acid,
saturated sodium bicarbonate, brine, dried, filtered and
25   concentrated to afford 420 mg of crude material. This
was chromatographed on 40 g of silica gel using 50% ethyl
acetate/hexane to afford 368 mg of pure benzamide, N-[2R-
hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)
amino]-1S-(phenylmethyl)propyl]-2-methyl, m/e=516(M+Li).
30
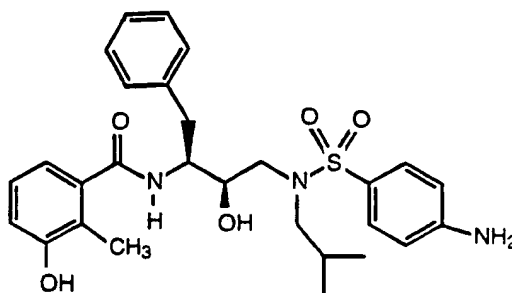
137

Example 18E

5   Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-
    aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
    (phenylmethyl)propyl]-3-hydroxy-2-methyl

    Part A: Preparation of 3-Hydroxy-2-methylbenzoic Acid
10

    A one-necked 100 mL round-bottomed flask (magnetic
    stirring) was charged with 1.0 gram (6.6 mM) 3-amino-2-
    methylbenzoic acid. A warm mixture of 2.3 mL conc.
    sulfuric acid in 4.3 mL water was added to the flask, the
15 resulting slurry was cooled below 15°C in an ice bath,
    and 6.6 grams of ice was added. The reaction mixture was
    treated via subsurface addition with a solution of 0.6
    gram (8.6 mM) sodium nitrite in 6.6 mL ice water with the
    reaction temperature maintained at 0-5°C during the
20 addition. After stirring at 0-5°C for 30 min., a few
    crystals of urea were added to decompose the excess
    nitrite. The reaction mixture was then poured into a
    room temperature solution of 23.8 grams (102.3 mM) copper
    (II) nitrate hemipentahydrate in 200 mL water. With
25 vigorous stirring, the reaction mixture was treated with
    0.9 gram (6.0 mM) copper (I) oxide. The reaction mixture
    foamed and changed from turquoise blue to dark green in
    color. Reaction was left stirring for 30 min. The
    reaction mixture was extracted with diethyl ether (3X),
30 and the organic extracts were combined. The organic
    extracts were concentrated to approximately one-fourth
    the original volume, then extracted with 25 mL 1N sodium

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hydroxide solution. The layers were separated, and the
dark-red aqueous layer was acidified to pH=2 using 1N
hydrochloric acid solution. The acidified aqueous layer
was then extracted with diethyl ether (3X), and the ether
5   extracts were combined, dried (MgSO4), and concentrated
to yield a reddish-colored oil. Purification by flash
chromatography on silica gel using a gradient of 0-7%
methanol/methylene chloride afforded 0.39 grams (36%) of
a yellow solid.
10

Part B: Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-
aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-3-hydroxy-2-methyl

15   To a solution of 175 mg (1.15 mmol) of 3-hydroxy-2-
methylbenzoic acid and 203 mg (1.5 mmol) of N-
hydroxybenzotriazole in 6 mL of anhydrous N,N-
dimethylformamide at 0°C, was added 220 mg (1.15 mmol) of
EDC. After 20 minutes of activation at 0°C and 1 hour at
20   room temperature, 392 mg (1.0 mmol) of 2R-hydroxy-3-[(2-
methylpropyl)(4-aminophenyl)sulfonyl]amino-1S-
(phenylmethyl)propylamine was added. After 15 hours at
room temperature, ethyl acetate was added, washed with 5%
citric acid, saturated sodium bicarbonate, brine, dried,
25   filtered and concentrated to afford 590 mg of crude
material. This was chromatographed on silica gel using
50-80% ethyl acetate/methylene chloride as eluent to
afford 255 mg of pure benzamide, N-[2R-hydroxy-3-[[(4-
aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
30   (phenylmethyl)propyl]-3-hydroxy-2-methyl, m/e = 526(M+H).

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Example 18F
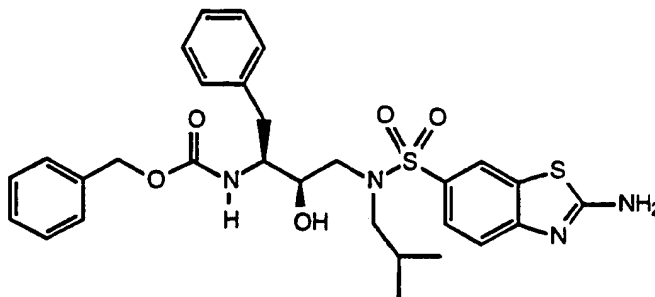
5   Preparation of Carbamic acid, 2R-hydroxy-3-[[(2-
    aminobenzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-
    1S-(phenylmethyl)propyl-, phenylmethyl ester

    Carbamic acid, 2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-
10 methylpropyl)amino]-1S-(phenylmethyl)propyl-,
    phenylmethyl ester 0.30 g (0.571 mmol) was added to a
    well mixed powder of anhydrous copper sulfate (1.20 g)
    and potassium thiocyanate (1.50 g) followed by dry
    methanol (6 mL) and the resulting black-brown suspension
15 was heated at reflux for 2 hrs. The reaction mixture was
    filtered and the filtrate was diluted with water (5 mL)
    and heated at reflux. Ethanol was added to the reaction
    mixture, cooled and filtered. The filtrate upon
    concentration afforded a residue which was
20 chromatographed (ethyl acetate:hexane 80:20) to afford
    0.26 g (78%) of the desired compound as a solid.

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Example 18G
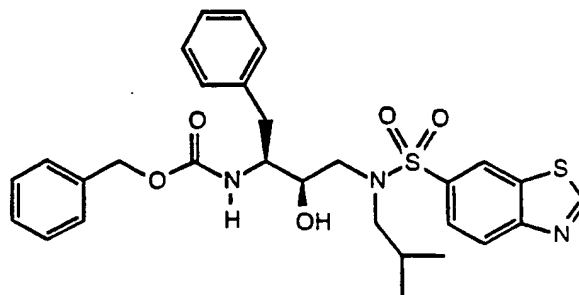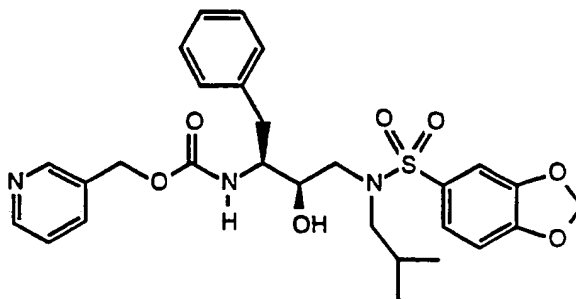

5   Preparation of Carbamic acid, 2R-hydroxy-3-
[[(benzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, phenylmethyl ester

Carbamic acid, 2R-hydroxy-3-[[(2-aminobenzothiazol-6-

10   yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)
propyl-, phenylmethyl ester (0.25 g, 0.429 mmol) was
added to a solution of isoamylnitrite (0.116 mL, 0.858
mmol) in dioxane (5 mL) and the mixture was heated at
85°C. After the cessation of evolution of nitrogen, the

15   reaction mixture was concentrated and the residue was
purified by chromatography (hexane:ethyl acetate 5:3) to
afford 0.130 g (53%) of the desired product as a solid.

Example 19A

20
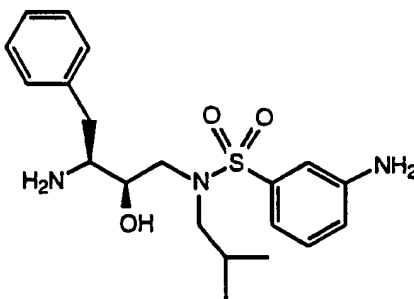
Preparation of 2R-hydroxy-3-[[(3-aminophenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propylamine

25

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Part A: Preparation of Carbamic acid, [2R-hydroxy-3-[(3-
nitrophenylsulfonyl)(2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, phenylmethyl ester

5   To a solution of 1.1 g (3.0 mmol) of N-[3S-benzyloxy
     carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in
     15mL of anhydrous methylene chloride, was added 1.3mL
     (0.94g, 9.3 mmol) of triethylamine. The solution was
     cooled to 0°C and 0.67 g (3.0 mmol) of 3-nitrobenzene
10   sulfonyl chloride was added, stirred for 30 minutes at
     0°C, then for 1 hour at room temperature. Ethyl acetate
     was added, washed with 5% citric acid, saturated sodium
     bicarbonate, brine, dried and concentrated to yield 1.74
     g of crude material. This was recrystallized from ethyl
15   acetate/hexane to afford 1.40 g of pure carbamic acid,
     [2R-hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl)
     amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester,
     m/e=562(M+Li).

20   Part B: Preparation of [2R-hydroxy-3-[[(3-
     aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
     (phenylmethyl)propylamine

     A solution of 1.33g (2.5 mmol) of carbamic acid, [2R-
25   hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl)amino]-
     1S-(phenylmethyl)propyl-, phenylmethyl ester in 40 mL of
     1:1 methanol/tetrahydrofuran was hydrogenated over 0.70 g
     of 10% palladium-on-carbon catalyst under 40 psig of
     hydrogen for 1.5 hours. The catalyst was removed by
30   filtration and the solution concentrated to afford 0.87 g
     of the desired [2R-hydroxy-3-[[(3-aminophenyl)sulfonyl]
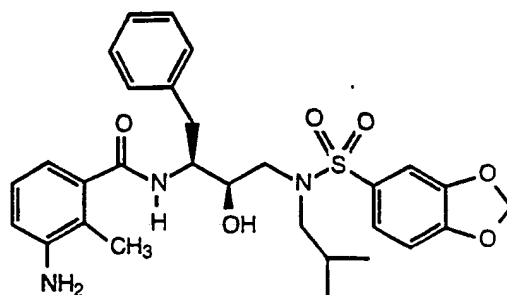   (2-methylpropyl)amino]-1S-(phenylmethyl)propylamine.

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Example 19B

5   <u>Preparation of Carbamic acid, 2R-hydroxy-3-[[(3-</u>
<u>aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-</u>
<u>(phenylmethyl)propyl-, 5-thiazolylmethyl ester</u>

To a solution of 133mg (1.15 mmol) of 5-(hydroxymethyl)
10   thiazole in 3 mL of anhydrous acetonitrile, was added
0.30 mL (0.29g, 3.7 mmol) of pyridine and then 296 mg
(1.15 mmol) of N,N'-disuccinimidyl carbonate at room
temperature under nitrogen. After 60 minutes, 460 mg
(1.18 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(3-
15   aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
was added. After stirring at room temperature for 15
hours, ethyl acetate was added, washed with 5% citric
acid, saturated sodium bicarbonate and brine, dried over
magnesium sulfate, filtered and concentrated to afford
20   480 mg of crude product. This was chromatographed on
silica gel using 50-80% ethyl acetate/hexane as eluent to
afford 422 mg of a white solid, which was identified as
the desired carbamic acid, 2R-hydroxy-3-[(3-aminophenyl
sulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-,
25   5-thiazolylmethyl ester, m/e = 539 (M+Li).

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<u>Example 19C</u>
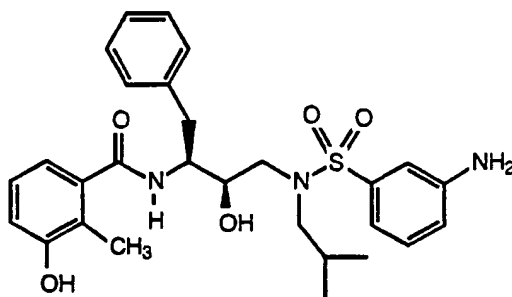
5   <u>Preparation of Benzamide, N-[2R-hydroxy-3-[[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl</u>

To a solution of 134 mg (0.88 mmol) of 3-hydroxy-2-

10   methylbenzoic acid and 155 mg (1.15 mmol) of N-hydroxybenzotriazole in 5 mL of anhydrous N,N-dimethylformamide at 0°C, was added 167 mg (0.88 mmol) of EDC. After 20 minutes of activation at 0°C and 1 hour at room temperature, 300 mg (1.0 mmol) of 2R-hydroxy-3-[(2-

15   methylpropyl)(3-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 15 hours at room temperature, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 330 mg of crude

20   material. This was chromatographed on silica gel using 30-70% ethyl acetate/methylene chloride as eluent to afford 230 mg of pure benzamide, N-[2R-hydroxy-3-[[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl.

25

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Example 19D

and
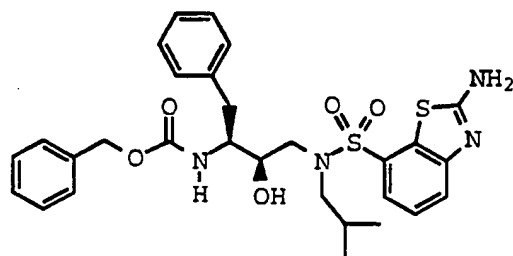
5   Preparation of Carbamic acid, 2R-hydroxy-3-[[(2-amino
    benzothiazol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-
    (phenylmethyl)propyl-, phenylmethyl ester; and Carbamic
    acid, 2R-hydroxy-3-[[(2-aminobenzothiazol-7-yl)sulfonyl]
    (2-methylpropyl)amino]-1S-(phenylmethyl)propyl-,
10 phenylmethyl ester

    The carbamic acid, 2R-hydroxy-3-[(3-aminophenylsulfonyl)
    (2-methylpropyl)amino]-1S-(phenylmethyl)propyl-,
    phenylmethyl ester 0.36 g (0.685 mmol) was added to a
15 well mixed powder of anhydrous copper sulfate (1.44 g)
    and potassium thiocyanate (1.80 g) followed by dry
    methanol (10 mL) and the rsulting black-brown suspension
    was heated at reflux for 2 hrs. The reaction mixture was
    filtered and the filtrate was diluted with water (5 mL)
20 and heated at reflux. Ethanol was added to the reaction
    mixture, cooled and filtered. The filtrate upon
    concentration afforded a rseidue which was
    chromatographed (ethyl acetate:hexane 1:1) to afford 0.18
    g (45%) of the 7-isomer as a solid. Further elution of

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the column with (ethyl acetate:hexane 3:2) afforded 0.80
g (20%) afforded the 5-isomer as a solid.

Example 20A
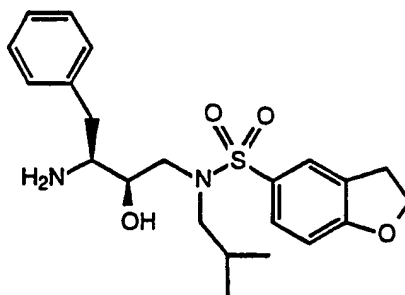
Preparation of 2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-
yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)
propylamine

Part A: Preparation of 5-(2,3-dihydrobenzofuranyl)
sulfonyl chloride

To a solution of 3.35g of anhydrous N,N-dimethylformamide
at 0°C under nitrogen was added 6.18 g of sulfuryl
chloride, whereupon a solid formed. After stirring for
15 minutes, 4.69 g of 2,3-dihydrobenzofuran was added,
and the mixture heated at 100°C for 2 hours. The
reaction was cooled, poured into ice water, extracted
with methylene chloride, dried over magnesium sulfate,
filtered and concentrated the crude material. This was
recrystallized from ethyl acetate to afford 2.45 g of 5-
(2,3-dihydrobenzofuranyl)sulfonyl chloride.

Part B: Preparation of Carbamic acid, 2R-hydroxy-3-
[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)
amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

To a solution of 1.11 g (3.0 mmol) of N-[3S-benzyloxy
carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in
20mL of anhydrous methylene chloride, was added 1.3mL

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(0.94 g, 9.3 mmol) of triethylamine. The solution was
cooled to 0°C and 0.66 g of 5-(2,3-dihydrobenzofuranyl)
sulfonyl chloride was added, stirred for 15 minutes at
0°C, then for 2 hour at room temperature. Ethyl acetate
5   was added, washed with 5% citric acid, saturated sodium
bicarbonate, brine, dried and concentrated to yield 1.62
g of crude material. This was recrystallized from
diethyl ether to afford 1.17 g of pure carbamic acid,
[2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-
10 methylpropyl)amino]-1S-(phenylmethyl)propyl-,
phenylmethyl ester.

Part C: Preparation of [2R-hydroxy-3-[[(2,3-dihydro
benzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-
15 (phenylmethyl)propylamine

A solution of 2.86 g of carbamic acid, [2R-hydroxy-3-
[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)
amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 30
20 mL of tetrahydrofuran was hydrogenated 0.99g of 10%
palladium-on-carbon under 50 psig of hydrogen for 16
hours. The catalyst was removed by filtration and the
filtrate concentrated to afford 1.99 g of the desired
[2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-
25 methylpropyl)amino]-1S-(phenylmethyl)propylamine.
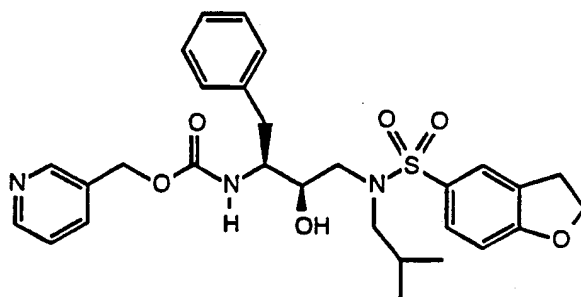
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Example 20B

5 Preparation of Carbamic acid, [2R-hydroxy-3-[[(2,3-
dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-
1S-(phenylmethyl)propyl-, 3-pyridylmethyl ester

To a solution of 110 mg of 3-pyridylcarbinol in 3 mL of
10 anhydrous acetonitrile, was added 0.24g of anhydrous
pyridine and then 260 mg of N,N'disuccinimidyl carbonate
at room temperature under nitrogen. After 45 minutes,
420 mg of 2R-hydroxy-3-[(2-methylpropyl)(2,3-
dihydrobenzofuran-5-yl)sulfonyl]amino-1S-(phenylmethyl)
15 propylamine was added. After stirring at room
temperature for 20 hours, ethyl acetate was added, washed
with 5% citric acid, saturated sodium bicarbonate and
brine, dried over magnesium sulfate, filtered and
concentrated to afford 320 mg of crude product. This was
20 chromatographed on silica gel using 50% ethyl
acetate/hexane as eluent to afford 260 mg of a white
solid, which was identified as the desired carbamic acid,
[2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-
25 pyridylmethyl ester.

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Example 20C
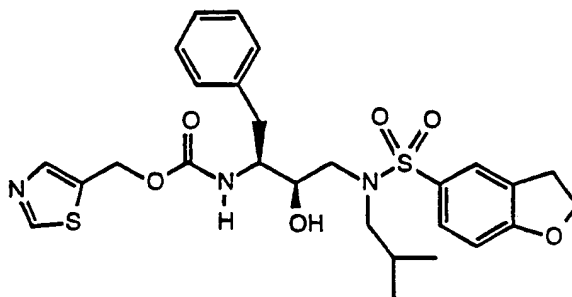
5   Preparation of Carbamic acid, [2R-hydroxy-3-[[(2,3-
    dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-
    1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester

    To a solution of 66 mg of 5-(hydroxymethyl)thiazole in 3
10 mL of anhydrous acetonitrile, was added 0.14g of
    anhydrous pyridine and then 150 mg of N,N'-disuccinimidyl
    carbonate at room temperature under nitrogen. After 45
    minutes, 240 mg of 2R-hydroxy-3-[(2-methylpropyl)(2,3-
    dihydrobenzofuran-5-yl)sulfonyl]amino-1S-(phenylmethyl)
15 propylamine was added. After stirring at room
    temperature for 20 hours, ethyl acetate was added, washed
    with 5% citric acid, saturated sodium bicarbonate and
    brine, dried over magnesium sulfate, filtered and
    concentrated to afford 220 mg of crude product. This was
20 chromatographed on silica gel using 50% ethyl
    acetate/hexane as eluent to afford 120 mg of a white
    solid, which was identified as the desired carbamic acid,
    [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-
    methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-
25 thiazolylmethyl ester.
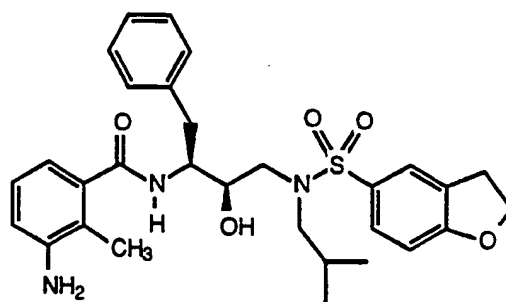
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Example 20D

5   <u>Preparation of Benzamide, N-[2R-hydroxy-3-[[(2,3-</u>
    <u>dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-</u>
    <u>1S-(phenylmethyl)propyl]-3-amino-2-methyl-</u>

    To a solution of 175 mg of 3-amino-2-methylbenzoic acid
10 in 2 mL of anhydrous N,N-dimethylformamide at 0°C, was
    added 200 mg of N-hydroxybenzotriazole and then 210 mg of
    EDC. After 20 minutes of activation, 405 mg of 2R-
    hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-
    methylpropyl)amino]-1S-(phenylmethyl)propylamine was
15 added. After stirring at room temperature for 16 hours,
    ethyl acetate was added, wshed with 5% citric acid,
    sodium bicarbonate, brine, dried over magnesium sulfate,
    filtered and concentrated to afford 225 mg of crude
    product. This was chromatographed on silica gel using
20 50% ethyl acetate/hexane to afford 140 mg of the desired
    benzamide, N-[2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-
    yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)
    propyl]-3-amino-2-methyl, m/e=552(M+H).

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Example 21A
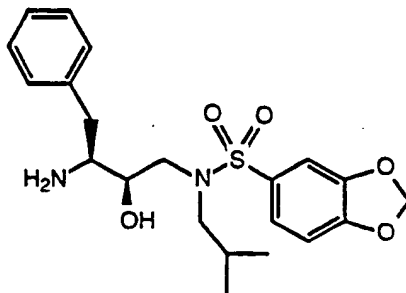
5   Preparation of 2R-hydroxy-3-[[(1,3-benzodioxol-5-
     yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)
     propylamine

     Part A: Preparation of (1,3-Benzodioxol-5-yl)sulfonyl
10   chloride

     To a solution of 4.25 g of anhydrous N,N-
     dimethylformamide at 0°C under nitrogen was added 7.84g
     of sulfuryl chloride, whereupon a solid formed. After
15   stirring for 15 minutes, 6.45 g of 1,3-benzodioxole was
     added, and the mixture heated at 100°C for 2 hours. The
     reaction was cooled, poured into ice water, extracted
     with methylene chloride, dried over magnesium sulfate,
     filtered and concentrated to give 7.32 g of crude
20   material as a black oil. This was chromatographed on
     silica gel using 20% methylene chloride/hexane to afford
     1.9 g of (1,3-benzodioxol-5-yl)sulfonyl chloride.

     Part B: Preparation of Carbamic acid, 2R-hydroxy-3-
25   [[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-
     1S-(phenylmethyl)propyl-, phenylmethyl ester

     To a solution of 3.19 g(8.6 mmol) of N-[3S-benzyloxy
     carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in
30   40mL of anhydrous methylene chloride, was added 0.87g of
     triethylamine. The solution was cooled to 0°C and 1.90g
     of (1,3-benzodioxol-5-yl)sulfonyl chloride was added,

stirred for 15 minutes at 0°C, then for 17 hours at room
temperature. Ethyl acetate was added, washed with 5%
citric acid, saturated sodium bicarbonate, brine, dried
and concentrated to yield crude material. This was
5   recrystallized from diethyl ether/hexane to afford 4.77 g
of pure carbamic acid, 2R-hydroxy-3-[[(1,3-benzodioxol-
5-yl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, phenylmethyl ester.

10   Part C: Preparation of 2R-hydroxy-3-[[(1,3-benzodioxol-
5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)
propylamine

A solution of 4.11 g of carbamic acid, 2R-hydroxy-3-
15   [[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-
1S-(phenylmethyl)propyl-, phenylmethyl ester in 45 mL of
tetrahydrofuran and 25 mL of methanol was hydrogenated
over 1.1 g of 10% palladium-on-carbon under 50 psig of
hydrogen for 16 hours. The catalyst was removed by
20   filtration and the filtrate concentrated to afford 1.82g
of the desired 2R-hydroxy-3-[[(1,3-benzodioxol-5-
yl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propylamine.

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Example 21B

5   Preparation of Carbamic acid, 2R-hydroxy-3-[[(1,3-
    benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-
    (phenylmethyl)propyl-, 3-pyridylmethyl ester

     To a solution of 110 mg of 3-pyridylcarbinol in 3 mL of
10   anhydrous acetonitrile, was added 0.24 g of anhydrous
     pyridine and then 260 mg of N,N'disuccinimidyl carbonate
     at room temperature under nitrogen. After 45 minutes,
     410 mg of 2R-hydroxy-3-[[(1,3-benzodioxol-5-
     yl)sulfonyl](2-methylpropyl)amino]-1S-
15   (phenylmethyl)propylamine was added. After stirring at
     room temperature for 20 hours, ethyl acetate was added,
     washed with 5% citric acid, saturated sodium bicarbonate
     and brine, dried over magnesium sulfate, filtered and
     concentrated to afford 330 mg of crude product. This was
20   chromatographed on silica gel using 50% ethyl
     acetate/hexane as eluent to afford 160 mg of a white
     solid, which was identified as the desired carbamic acid,
     [2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-
     methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-
25   pyridylmethyl ester, m/e=562(M+Li).

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Example 21C
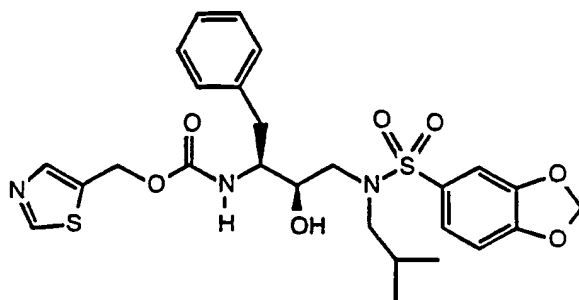
Preparation of Carbamic acid, 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester

To a solution of 85 mg (0.8 mmol) of 5-(hydroxymethyl) thiazole in 2.2 mL of anhydrous acetonitrile, was added 0.18 mL (2.2 mmol) of anhydrous pyridine and then 189 mg (0.74 mmol) of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 310 mg of 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 20 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 300 mg of crude product. This was chromatographed on silica gel using 50% ethyl acetate/hexane as eluent to afford 150 mg of a white solid, which was identified as the desired carbamic acid, 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester, m/e=568(M+Li).

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Example 21D

5   <u>Preparation of Benzamide, N-[2R-hydroxy-3-[[(1,3-
     benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-
     (phenylmethyl)propyl]-3-amino-2-methyl</u>

     To a solution of 175 mg of 3-amino-2-methylbenzoic acid
10   in 2 mL of anhydrous N,N-dimethylformamide at 0°C, was
     added 200 mg of N-hydroxybenzotriazole and then 210 mg of
     EDC. After 20 minutes of activation, 410 mg of 2R-
     hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-
     methylpropyl)amino]-1S-(phenylmethyl)propylamine was
15   added. After stirring at room temperature for 16 hours,
     ethyl acetate was added, washed with 5% citric acid,
     sodium bicarbonate, brine, dried over magnesium sulfate,
     filtered and concentrated to afford 500 mg of crude
     product. This was chromatographed on silica gel using
20   50% ethyl acetate/hexane to afford 310 mg of the desired
     benzamide, N-[2R-hydroxy-3-[[(1,3-benzodioxol-5-
     yl)sulfonyl](2-methylpropyl)amino]-1S-
     (phenylmethyl)propyl]-3-amino-2-methyl, m/e=560(M+Li).

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Example 21E
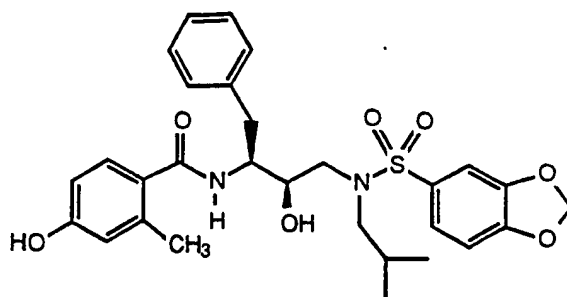
5   Preparation of Benzamide, N-[2R-hydroxy-3-[[(1,3-
     benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-
     (phenylmethyl)propyl]-4-hydroxy-2-methyl

     Part A: Preparation of 2-Trimethylsilyloxy-1,3-
10   cyclohexadiene

     A 100 mL round bottom flask equipped with magnetic stir
     bar, addition funnel, and N_2 inlet was charged with 40 mL
     dry THF and 8.3 mL diisopropyl amine. The solution was
15   cooled to -78°C and charged with 23.8 mL of 2.5M nBuLi in
     Hexane. After 10 minutes a solution of 5.2 g
     cyclohexenone in 10 mL THF was added dropwise. The
     reaction was stirred 10 minutes at -78°C and quenched
     with 7.5 mL trimethylsilyl chloride. The reaction was
20   stirred 15 minutes and then partitioned between diethyl
     ether and cold saturated aqueous sodium bicarbonate. The
     combined organic layers were dried over sodium sulfate
     and concentrated in vacuo to a yellow oil. Short path
     distillation (BP 27-29°C/0.5mm) afforded 6.0 g (66%) of
25   2-Trimethylsilyloxy-1,3-Cyclohexadiene.

     Part B: Preparation of Methyl (2-methyl-4-
     trimethylsilyoxy)benzoate

30   A 50 mL round bottom flask equipped with magnetic stir
     bar and condenser was charged with 6.0 g of 2-
     trimethylsilyloxy-1,3-cyclohexadiene, 3.5 g methyl

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tetrolate in 3 mL dry toluene. The reaction was heated
to 150°C for 50 hours at which point ¹H-NMR indicated no
starting diene. The raction was concentrated in vacuo to
provide 5.7 g (67%) methyl 2-methyl-4-
5   trimethylsilyloxybenzoate.

Part C: Preparation of 4-Hydroxy-2-methylbenzoic acid

A 100mL round bottom flask equipped with magnetic stir
10   bar was charged with 5.7 g methyl 2-methyl-4-
trimethylsilyloxybenzoate and 2.0 g LiOH in 40 mL
methanol and 10 mL water. After 2 hours at reflux the
reaction was poured into 10 mL concentrated HCl and then
100 g ice. Extraction with ethyl acetate followed by
15   concentration in vacuo gave a crude solid (70:30)
product:starting material. Flash Chromatography using
50-50 ethyl acetate/hexanes as an eluent gave 1.15 g 2-
methyl-4-hydroxybenzoic acid, m/e=193(M+H).

20   Part D: Preparation of Benzamide, N-[2R-hydroxy-3-
[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-
1S-(phenylmethyl)propyl]-4-hydroxy-2-methyl

To a solution of 175 mg of 4-hydroxy-2-methylbenzoic acid
25   in 2 mL of anhydrous N,N-dimethylformamide at 0°C, was
added 200 mg of N-hydroxybenzotriazole and then 220 mg of
EDC. After 20 minutes of activation, 450 mg of 2R-
hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propylamine was
30   added. After stirring at room temperature for 16 hours,
ethyl acetate was added, wshed with 5% citric acid,
sodium bicarbonate, brine, dried over magnesium sulfate,
filtered and concentrated to afford crude product. This
was chromatographed on silica gel using 50% ethyl
35   acetate/hexane to afford 102 mg of the desired benzamide,
N-[2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-4-hydroxy-2-
methyl.

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Example 21F

5
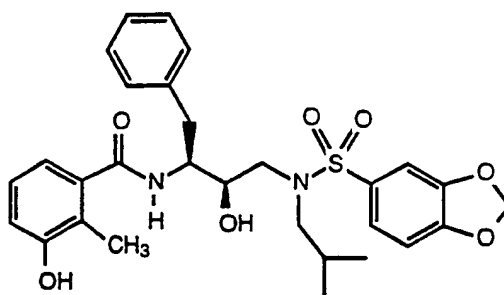
Preparation of Benzamide, N-[2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl

10   To a solution of 187 mg (1.23 mmol) of 3-hydroxy-2-methylbenzoic acid and 217 mg (1.61 mmol) of N-hydroxybenzotriazole in 6 mL of anhydrous N,N-dimethylformamide at 0°C, was added 236 mg (1.23 mmol) of EDC. After 20 minutes of activation at 0°C and 1 hour at
15   room temperature, 450 mg (1.07 mmol) of 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine was added. After 15 hours at room temperature, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine,
20   dried, filtered and concentrated to afford 650 mg of crude material. This was chromatographed on silica gel using 0-25% ethyl acetate/methylene chloride as eluent to afford 390 mg of pure benzamide, N-[2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-
25   (phenylmethyl)propyl]-3-hydroxy-2-methyl, m/e=561(M+Li).

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Example 22

Following the procedures of Examples 1-21, the compounds shown in Tables 3, 5A and 5B were prepared and in Tables 4 through 17 can be prepared.

TABLE 3
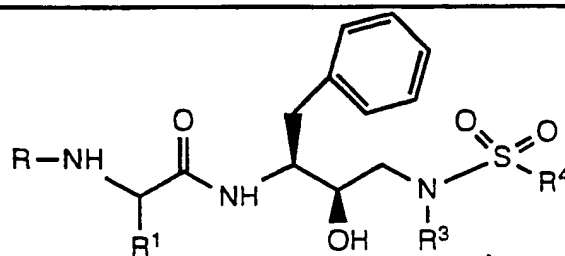
Entry No.	R	R^1	R^3	R^4
1	Cbz	t-Butyl	i-Amyl	Methyl
2	N,N-Dimethylglycine	t-Butyl	i-Amyl	Methyl
3	Cbz	i-Propyl	i-Amyl	Phenyl
4	Cbz	sec-Butyl	i-Amyl	Phenyl
5	Cbz	$CH_2C(O)NH_2$	n-Propyl	Phenyl
6	N-Methylglycine	t-Butyl	i-Amyl	Phenyl
7	Cbz	t-Butyl	i-Butyl	Phenyl
8	N,N-Dimethylglycine	t-Butyl	i-Amyl	Phenyl
9	N-Methylglycine	t-Butyl	i-Amyl	Phenyl
10	N,N-Dimethylglycine	t-Butyl	i-Butyl	$(4-OCH_3)$Phenyl
11	N-Methylglycine	t-Butyl	i-Butyl	$(4-OCH_3)$Phenyl

TABLE 4
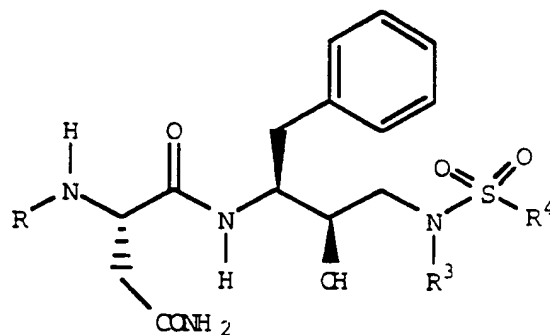
	Entry No.	R	R^3	R^4
10	1	Cbz[a]	CH_3	n-Butyl
	2	Cbz	i-Butyl	CH_3
	3	Cbz	i-Butyl	n-Butyl
	4	Q[b]	i-Butyl	n-Butyl
	5	Cbz	i-Propyl	n-Butyl
15	6	Q	i-Propyl	n-Butyl
	7	Cbz	C_6H_5	n-Butyl
	8	Cbz	-CH_2-⬡	n-Butyl
	9	Cbz	-CH_2-⬡	n-Butyl
	10	Q	-CH_2-⬡	n-Butyl
20	11	Cbz	-⬡	n-Butyl
	12	Cbz	i-Butyl	n-Propyl

TABLE 4 (Cont'd.)
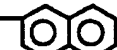
Entry No.	R	R^3	R^4
13	Cbz	i-Butyl	$-CH_2CH(CH_3)_2$
14	Cbz	(R)-CH(CH_3)-phenyl	n-Butyl
15	Cbz	CH_2-cyclohexyl	i-Propyl
16	Cbz	$-CH_2$-cyclohexyl	$-CH_2CH_2CH(CH_3)_2$
17	Cbz	i-Butyl	$-CH_2CH_3$
18	Cbz	i-Butyl	$-CH(CH_3)_2$
19	Cbz	i-Butyl	cyclohexyl
20	Q	-Butyl	cyclohexyl
21	Cbz	$-CH_2$-cyclohexyl	$-(CH_2)_2CH(CH_3)_2$
22	Cbz	$(CH_2)_2CH(CH_3)_2$	$-CH(CH_3)_2$
23	Q	i-Butyl	$-CH(CH_3)_2$
24	Cbz	i-Butyl	$-C(CH_3)_3$
25	Q	i-Butyl	$-C(CH_3)_3$
26	Cbz	$-CH_2$-naphthyl	$-C(CH_3)_3$
27	Q	$-CH_2$-naphthyl	$-C(CH_3)_3$
28	Cbz	$-(CH_2)_2CH(CH_3)_2$	$-C(CH_3)_3$
29	Q	$-(CH_2)_2CH(CH_3)_2$	$-C(CH_3)_3$
30	Cbz	$-CH_2C_6H_5$	$-C(CH_3)_3$
31	Q	$-CH_2C_6H_5$	$-C(CH_3)_3$
32	Cbz	$-(CH_2)_2C_6H_5$	$-C(CH_3)_3$
33	Cbz	$-(CH_2)_2C_6H_5$	$-C(CH_3)_3$
34	Cbz	n-Butyl	$-C(CH_3)_3$

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TABLE 4 (Cont'd.)
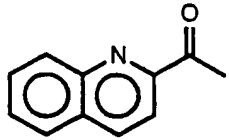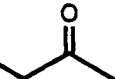
Entry No.	R	R³	R⁴
35	Cbz	n-Pentyl	-C(CH₃)₃
36	Cbz	n-Hexyl	-C(CH₃)₃
37	Cbz	-CH₂-⟨phenyl⟩	-C(CH₃)₃
38	Cbz	-CH₂C(CH₃)₃	-C(CH₃)₃
39	Q	-CH₂C(CH₃)₃	-C(CH₃)₃
40	Cbz	-CH₂CH₂-N⟨morpholine-O⟩	-C(CH₃)₃
41	Cbz	-CH₂C₆H₅OCH₃ (para)	-C(CH₃)₃
42	Cbz	-CH₂-⟨pyridinyl (N top)⟩	-C(CH₃)₃
43	Cbz	-CH₂-⟨pyridinyl (O,N)⟩	-C(CH₃)₃
44	Cbz	-(CH₂)₂C(CH₃)₃	-C(CH₃)₃
45	Q	-(CH₂)₂C(CH₃)₃	-C(CH₃)₃
46	Cbz	-(CH₂)₄OH	-C(CH₃)₃
47	Q	-(CH₂)₄OH	-C(CH₃)₃
48	Q	-CH₂-⟨C₆H₄⟩-F	-C(CH₃)₃
49	Q	-CH₂-⟨pyridinyl (N)⟩	-C(CH₃)₃
50	Cbz	-CH₂CH(CH₃)₂	-C₆H₅
51	⟨quinolin-2-yl-C(=O)CH₃⟩	-CH₂CH(CH₃)₂	-C₆H₅
52	(CH₃)₂N-CH₂-C(=O)-	-CH₂CH(CH₃)₂	-C₆H₅

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TABLE 4 (Cont'd.)

Entry No.	R	R³	R⁴
53		$-CH_2CH(CH_3)_2$	$-C_6H_5$
54		$-CH_2CH(CH_3)_2$	$-C_6H_5$
55		$-CH_2CH(CH_3)_2$	$-C_6H_5$
56		$-CH_2CH(CH_3)_2$	$-C_6H_5$
57		$-CH_2CH(CH_3)_2$	$-C_6H_5$
58		$-CH_2CH(CH_3)_2$	$-C_6H_5$
59		$-CH_2CH(CH_3)_2$	$-C_6H_5$

TABLE 4 (Cont'd.)
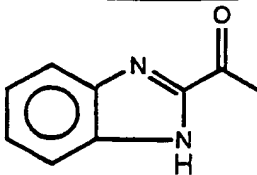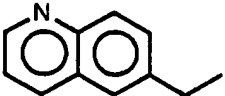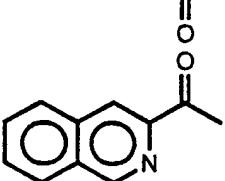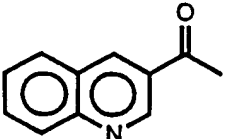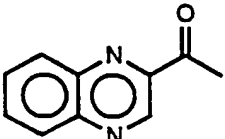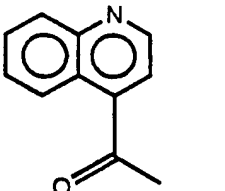
Entry No.	R	R^3	R^4
60		$-CH_2CH(CH_3)_2$	$-C_6H_5$
61		$-CH_2CH(CH_3)_2$	$-C_6H_5$
62		$-CH_2CH(CH_3)_2$	$-C_6H_5$
63		$-CH_2CH(CH_3)_2$	$-C_6H_5$
64		$-CH_2CH(CH_3)_2$	$-C_6H_5$
65		$-CH_2CH(CH_3)_2$	$-C_6H_5$

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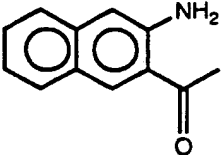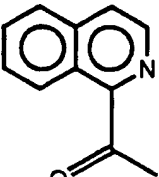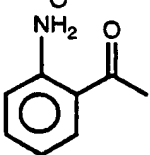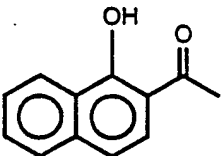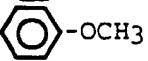
TABLE 4 (Cont'd.)

Entry No.	R	R³	R⁴
66		$-CH_2CH(CH_3)_2$	$-C_6H_5$
67		$-CH_2CH(CH_3)_2$	$-C_6H_5$
68		$-CH_2CH(CH_3)_2$	$-C_6H_5$
69		$-CH_2CH(CH_3)_2$	$-C_6H_5$
70	Q	$-CH_2Ph$	$-Ph$
71	Q	$-CH_2-$$-F$	$-Ph$
72	Q	$-CH_2-$	$-Ph$
73	Q	$-CH_2-$$-OCH_3$	$-Ph$
74	Q	$-CH_2-$	$-Ph$

TABLE 4 (Cont'd.)

Entry No.	R	R³	R⁴
75	Q	$-CH_2$—(cyclopropyl)	$-Ph$
76	Q	$-CH_2CH=CH_2$	$-Ph$
77	Q	$-$(phenyl)	$-Ph$
78	Q	$-$(cyclohexyl)	$-Ph$
79	Q	$-CH_2CH_2Ph$	$-Ph$
80	Q	$-CH_2CH_2CH_2CH_2OH$	$-Ph$
81	Q	$-CH_2CH_2N(CH_3)_2$	$-Ph$
82	Q	$-CH_2CH_2-N$(morpholino)O	$-Ph$
83	Q	$-CH_3$	$-Ph$
84	Q	$-CH_2CH_2CH_2SCH_3$	$-Ph$
85	Q	$-CH_2CH_2CH_2S(O)_2CH_3$	$-Ph$
86	Q	$-CH_2CH_2CH_2CH(CH_3)_2$	$-$(cyclohexyl)
87	Q	$-CH_2CH_2CH(CH_3)_2$	$-CH_2-$(phenyl)
88	Q	$-CH_2CH_2CH(CH_3)_2$	$-CH_2CH_2CH_3$
89	Q	$-CH_2CH_2CH_2CH(CH_3)_2$	$-CH_3$
90	Q	$-CH_2CH_2CH(CH_3)_2$	$-$(phenyl)$-F$
91	Q	$-CH_2CH_2CH(CH_3)_2$	(methylnaphthyl)
92	Q	$-CH_2CH_2CH(CH_3)_2$	$-$(phenyl)$-NO_2$
93	Q	$-CH_2CH_2CH(CH_3)_2$	(thienyl, S)
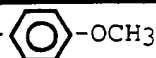
166

TABLE 4 (Cont'd.)

Entry No.	R	R^3	R^4
94	Q	$-CH_2CH_2CH(CH_3)_2$	phenyl, $-OCH_3$
95	Q	$-CH_2CH_2CH(CH_3)_2$	phenyl, NO_2
96	Q	$-CH_2CH_2CH(CH_3)_2$	phenyl, NO_2
97	Q	$-CH_2CH_2CH(CH_3)_2$	phenyl, CF_3
98	Q	$-CH_2CH_2CH(CH_3)_2$	phenyl, $-NHAc$
99	Q	$-CH_2CH_2CH(CH_3)_2$	phenyl, $-Cl$
100	Q	$-CH_2CH_2CH(CH_3)_2$	phenyl, $-CH_3$
101	Q	$-CH_2CH_2CH(CH_3)_2$	phenyl, CO_2CH_3
102	Q	$-CH_2CH_2CH(CH_3)_2$	phenyl
103	Q	$-CH_2CH(CH_3)_2$	phenyl, $-F$
104	Q	$-CH_2CH(CH_3)_2$	phenyl, $-NHAc$
105	Q	$-CH_2CH(CH_3)_2$	phenyl, $-CH_3$
106	Q	$-CH_2CH_2CH_3$	phenyl, $-OCH_3$
107	Q	$-CH_2CH_2CH_2CH_3$	phenyl, $-OCH_3$

a benzyloxycarbonyl

b 2-quinolinylcarbonyl

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TABLE 5

Entry	A	R³	R⁴
1	Cbz-Val	i-amyl	$-C_6H_5$
2	Cbz-Leu	i-amyl	$-C_6H_5$
3	Cbz-Ile	i-amyl	$-C_6H_5$
4	Ac-D-homo-Phe	i-Bu	methyl
5	Qui-Orn(g-Cbz)	$-CH_2-\bigcirc$	$-C_6H_5$
6	Cbz-Asn	$-CH_2CH=CH_2$	$-C_6H_5$
7	Acetyl-t-BuGly	i-amyl	$-C_6H_5$
8	Acetyl-Phe	i-amyl	$-C_6H_5$
9	Acetyl-Ile	i-amyl	$-C_6H_5$
10	Acetyl-Leu	i-amyl	$-C_6H_5$
11	Acetyl-His	i-amyl	$-C_6H_5$
12	Acetyl-Thr	i-amyl	$-C_6H_5$
13	Acetyl-NHCH(C(CH₃)₂(SCH₃))C(O)-	i-amyl	$-C_6H_5$
14	Cbz-Asn	i-amyl	$-C_6H_5$
15	Cbz-Ala	i-amyl	$-C_6H_5$
16	(N,N-dimethylglyciniyl)Val	i-amyl	$-C_6H_5$
17	(N-methylglyciniyl)Val	i-amyl	$-C_6H_5$
18	(N,N-dimethylglyciniyl)Ile	i-amyl	$-C_6H_5$
19	(N-methylglyciniyl)Ile	i-amyl	$-C_6H_5$

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TABLE 5 (Cont'd)

Entry	A	R³	R⁴
20	Cbz-Ala	i-amyl	-C₆H₅
21	Cbz-beta-cyanoAla	i-amyl	-C₆H₅
22	Cbz-t-BuGly	i-amyl	-C₆H₅
23	Q-t-BuGly	i-amyl	-C₆H₅
24	Q-SCH₃Cys	i-amyl	-C₆H₅
25	Cbz-SCH₃Cys	i-amyl	-C₆H₅
26	Q-Asp	i-amyl	-C₆H₅
27	Cbz-(NHCH(C(CH₃)₂(SCH₃))C(O)-	i-amyl	-C₆H₅
28	Cbz-EtGly	i-amyl	-C₆H₅
29	Cbz-PrGly	i-amyl	-C₆H₅
30	Cbz-Thr	i-amyl	-C₆H₅
31	Q-Phe	i-amyl	-C₆H₅
32	Cbz-Phe	i-amyl	-C₆H₅
33	CH2=CHCH2-O-C(=O)-	i-Butyl	-C₆H₄ (with OCH₃)

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TABLE 5A

Entry
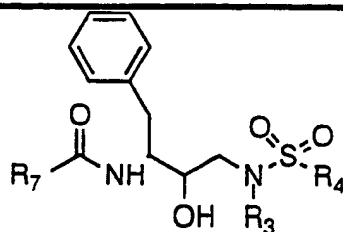
MASS MEASUREMENT

	R³	R⁴	R⁷	MOL FORM	CALC M+H	FOUND
1				$C_{27}H_{38}N_2O_5S$	503.2661	503.2624
2				$C_{28}H_{40}N_2O_5S$	517.2736	517.2777
3				$C_{29}H_{42}N_2O_5S$	531.2893	531.2916
4				$C_{32}H_{40}N_2O_5S$	565.2736	565.2731
5				$C_{30}H_{35}N_3O_5S$	550.2376	550.2427

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TABLE 5A (Cont'd)

Entry

5
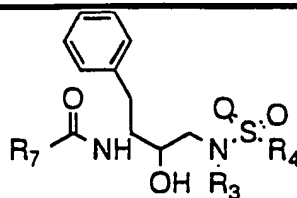
	R^3	R^4	R^7	MASS MEASUREMENT		
				MOL FORM	CALC	FOUND
6	CH$_2$CH(CH$_3$)CH$_3$	—⟨4-OCH$_3$-phenyl⟩	2,4,5-trimethylphenyl CH$_2$	C$_{30}$H$_{38}$N$_2$O$_5$S	539(M+H)	539
7			2,4-dimethylphenyl	C$_{29}$H$_{36}$N$_2$O$_5$S	?	?
8				C$_{30}$H$_{38}$N$_2$O$_5$S	539.2580 (M+H)	539.2591

TABLE 5A (Cont'd)

Entry

5

MASS MEASUREMENT
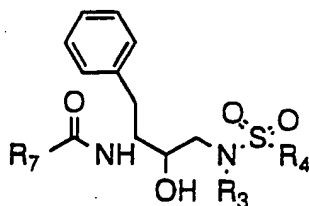
	R^3	R^4	R^7	MOL FORM	CALC (M+H)	FOUND
9	$CH_2\text{-}CH(CH_3)CH_3$	4-OCH_3-phenyl	pyridin-3-yl	$C_{27}H_{33}N_3O_5S$	512.2219	512.2271
10			2-methylpyridin-3-yl	$C_{28}H_{35}N_3O_5S$	526.2376	526.2388
11			pyridin-4-yl	$C_{27}H_{33}N_3O_5S$	512.2219	512.2287
12			2-Cl-phenyl	$C_{28}H_{33}N_2O_5ClS$	545.1877	545.1887
13			2-CH_2CH_3-phenyl	$C_{30}H_{38}N_2O_5S$	539.2580	539.2592
14			2-CH_2(CH_3)_2-phenyl	$C_{31}H_{40}N_2O_5S$	553.2736	553.2714
15			2,3-(CH_3)_2-phenyl	$C_{30}H_{38}N_2O_5S$	539.2580	539.2632
16			2,3-(CH_3)_2-phenyl	$C_{30}H_{38}N_2O_5S$	539 (M+H)	539

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TABLE 5A (Cont'd)

Entry

5
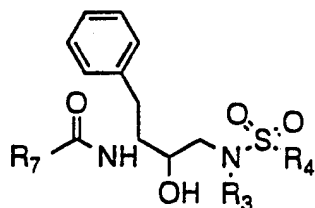
MASS MEASUREMENT

Entry	R^3	R^4	R^7	MOL FORM	CALC	FOUND
17	CH_2 isobutyl (CH_3, CH_3)	4-OCH_3 phenyl	phenyl, 2-SO_2CH_3	$C_{29}H_{36}N_2O_7S_2$	589.2042	589.2086 (M+H)
18			phenyl, 3-H_3CSO_2	$C_{29}H_{36}N_2O_7S_2$	595.2124	595.2103 (M+Li)
19			4-H_3CSO_2 phenyl	$C_{29}H_{36}N_2O_7S_2$	595.2124	595.2191 (M+Li)
20			phenyl, 2-$CH_2SO_2CH_3$	$C_{30}H_{38}N_2O_7S_2$	609.2281	609.2313 (M+Li)
21			phenyl, 3-$H_3CSO_2CH_2$	$C_{30}H_{38}N_2O_7S_2$	603.2199	603.2247 (M+H)
22			4-$H_3CSO_2CH_2$ phenyl	$C_{30}H_{38}N_2O_7S_2$	603.2199	603.2266 (M+H)

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TABLE 5A (Cont'd)

Entry

5

EXACT MASS MEASUREMENT

	R^3	R^4	R^7	MOL FORM	CALC (M+H)	FOUND
23	CH2–CH(CH3)–CH3	(benzyl) phenyl-CH2	phenyl			
24	CH2–CH(CH3)2 (isobutyl)	phenyl	phenyl	C27H32N2O4S	481.2161	481.2213
25	CH2–CH(CH3)2 (isobutyl)	4-OCH3-phenyl-CH2	phenyl	C28H35N2O5S	511.2267	511.2319
26	CH2–CH(CH3)2 (isobutyl)	4-OCH3-phenyl-CH2	2-CH3-phenyl	C29H36N2O5S	525.2423	525.2469
27			3-CH3-phenyl	C29H36N2O5S	525.2428	525.2464
28			4-CH3-phenyl (H3C–phenyl)	C29H36N2O5S	525.2423	525.2432
29			2-OCH3-phenyl	C29H36N2O6S	541.2372	541.2332
30			3-OCH3-phenyl (H3CO–phenyl)	C29H36N2O6S	541.2372	541.2355
31			4-OCH3-phenyl (H3CO–phenyl)	C29H36N2O6S	541.2372	541.2329

TABLE 5B

Entry A	Molecular Formula	Mass Spectrum
(3-NO2, 2-CH3 benzoyl)	$C_{29}H_{35}N_3O_7S$	576 (M+Li)
(3-NH2, 2-CH3 benzoyl)	$C_{29}H_{37}N_3O_5S$	540 (M+H)
(3-NMe2, 2-CH3 benzoyl)	$C_{31}H_{41}N_3O_5S$	568 (M+H)
(4-O2N, 2-CH3 benzoyl)	$C_{29}H_{35}N_3O_7S$	570 (M+H)
(4-H2N, 2-CH3 benzoyl)	$C_{29}H_{37}N_3O_5S$	540 (M+H)

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TABLE 5B (contd.)

5
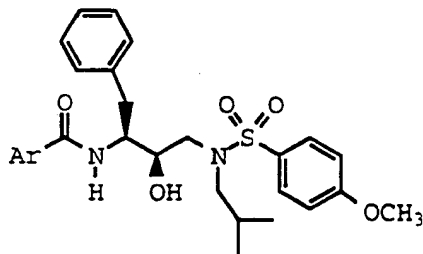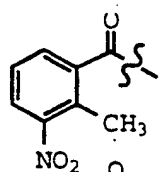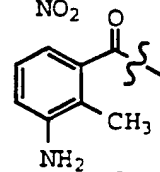
Entry A	Molecular Formula	Mass Spectrum
$C_{31}H_{41}N_3O_5S$	568 (M+H)
$C_{29}H_{35}N_3O_7S$	570 (M+H)
$C_{29}H_{37}N_3O_5S$	546 (M+Li)
$C_{31}H_{41}N_3O_5S$	574 (M+Li)

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TABLE 6
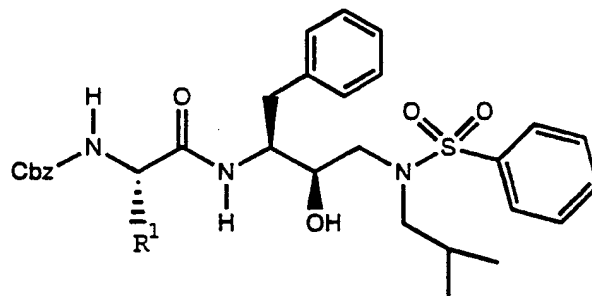
Entry	R¹
1	$CH_2SO_2CH_3$
2	$(R)-CH(OH)CH_3$
3	$CH(CH_3)_2$
4	$(R,S)CH_2SOCH_3$
5	$CH_2SO_2NH_2$
6	CH_2SCH_3
7	$CH_2CH(CH_3)_2$
8	$CH_2CH_2C(O)NH_2$
9	$(S)-CH(OH)CH_3$
10	$-CH_2C\equiv C-H$

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TABLE 7
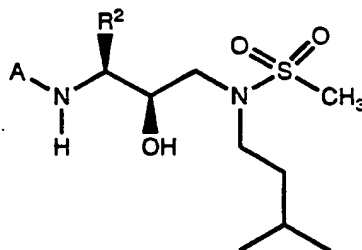
Entry	R^2	A
1	n-Bu	Cbz-Asn
2	cyclohexylmethyl	Cbz-Asn
3	n-Bu	Boc
4	n-Bu	Cbz
5	C$_6$H$_5$CH$_2$	Boc
6	P-F-C$_6$H$_5$CH$_2$	Cbz
7	C$_6$H$_5$CH$_2$	benzoyl
8	cyclohexylmethyl	Cbz
9	n-Bu	Q-Asn
10	cyclohexylmethyl	Q-Asn
11	C$_6$H$_5$CH$_2$	Cbz-Ile
12	C$_6$H$_5$CH$_2$	Q-Ile
13	P-F-C$_6$H$_5$CH$_2$	Cbz-t-BuGly
14	C$_6$H$_5$CH$_2$	Q-t-BuGly
15	C$_6$H$_5$CH$_2$	Cbz-Val
16	C$_6$H$_5$CH$_2$	Q-Val
17	2-naphthylmethyl	Cbz-Asn
18	2-naphthylmethyl	Q-Asn
19	2-naphthylmethyl	Cbz
20	n-Bu	Cbz-Val
21	n-Bu	Q-Val
22	n-Bu	Q-Ile
23	n-Bu	Cbz-t-BuGly

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TABLE 7 (Cont'd)
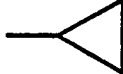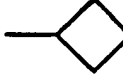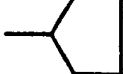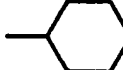
Entry	R^2	A
24	n-Bu	Q-t-BuGly
25	p-F$(C_6H_4)CH_2$	Q-Asn
26	p-F$(C_6H_4)CH_2$	Cbz
27	p-F$(C_6H_4)CH_2$	Cbz-Asn
28	$C_6H_5CH_2$	Cbz-propargylglycine
29	$C_6H_5CH_2$	Q-propargylglycine
30	$C_6H_5CH_2$ acetylpropargylglycine	

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TABLE 8
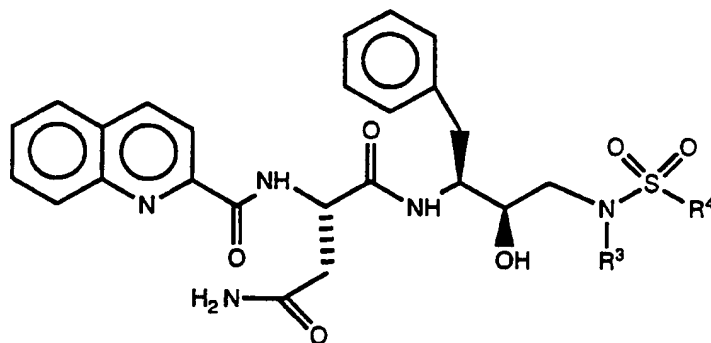
Entry	R³	R⁴
1	$-CH_2CH(CH_3)_2$	$-C(CH_3)_2$
2	$-CH_2CH_2CH(CH_3)_2$	(cyclopropyl)
3	$-CH_2CH_2CH(CH_3)_2$	(cyclobutyl)
4	$-CH_2CH_2CH(CH_3)_2$	(cyclopentyl)
5	$-CH_2CH_2CH(CH_3)_2$	(cyclohexyl)

TABLE 9

Entry	R	R^1
1	(4-methoxybenzyl acetate structure)	-CH$_3$
2	(acetone/isopropyl ketone structure)	-CH$_3$
3	(4-methoxybenzyl acetate structure)	-CH(CH$_3$)$_2$
4	(acetone/isopropyl ketone structure)	-CH(CH$_3$)$_2$
5	(benzyl acetate structure)	-C(CH$_3$)$_3$
6	(naphthyl-OCH$_2$-C- structure)	-CH$_3$
7	(phenoxy-CH$_2$-C- structure)	-CH$_3$

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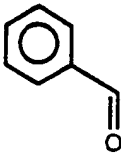
Table 9 (Cont'd)

Entry	R	R^1
8	$HO_2CCH_2CH_2$-C(=O)-	-CH$_3$
9	(benzaldehyde structure)	-CH$_3$
10	CH_3NH-C(=O)-	-CH$_3$
11	$(CH_3)_2CH$-C(=O)-	-CH$_3$
12	CH_3OCH_2-C(=O)-	-CH$_3$
13	$(CH_3)_2NCH_2$-C(=O)-	-CH$_3$
14	$CH_3CH(OH)$-C(=O)-	-CH$_3$

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TABLE 9 (Cont'd)

5 Entry

15

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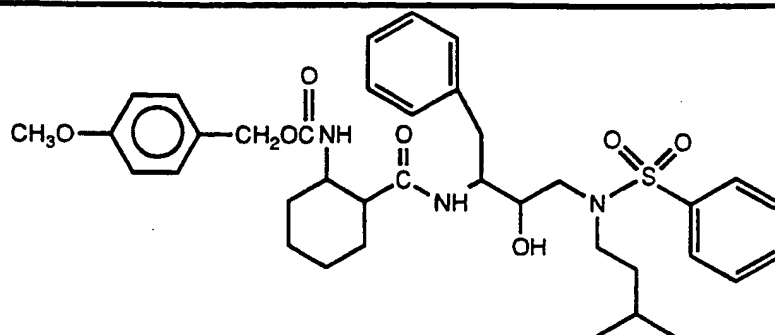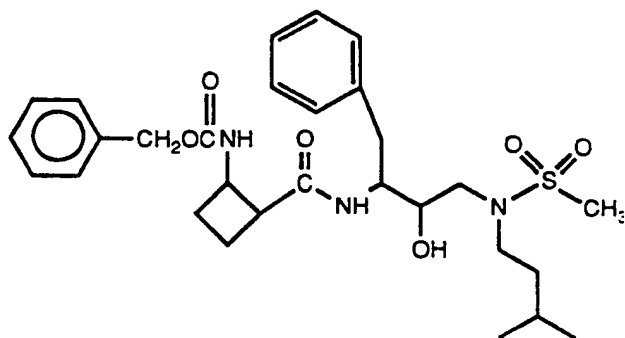
TABLE 10
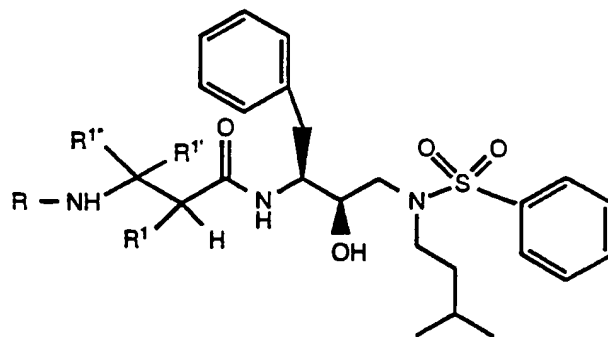
Entry	R¹	R¹'	R¹"	R
1	H	H	H	
2	H	H	H	
3	H	CH₃	H	
4	H	CH₃	CH₃	
5	H	H	CO₂CH₃	
6	H	H	H	
7	H	H	H	
8	H	H	CONH₂	Cbz
9	H	H	CONH₂	2-quinolinylcarbonyl

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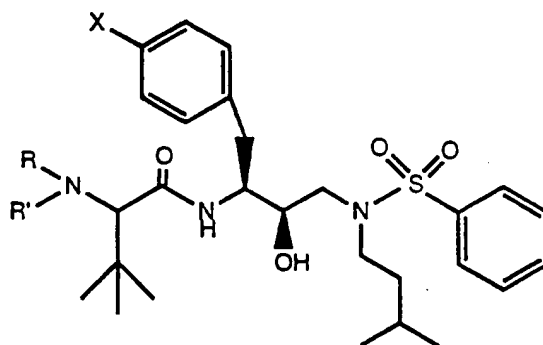
TABLE 11

Entry	R	R'	X
1	R=H	R'=H	X=H
2	R=Me	R'=Me	X=H
3	R=H	R'=Me	X=H
4	R=Me	R'=Me	X=F
5	R=H	R'=Me	X=F
6	R=Cbz	R'=Me	X=H
7	R=H	R'=Bz	X=H
8	R+R'=pyrrole	X=H	

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TABLE 12
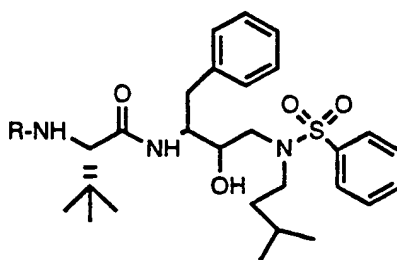
Entry	Acyl Group (R)
1	benzyloxycarbonyl
2	tert-butoxycarbonyl
3	acetyl
4	2-quinoylcarbonyl
5	phenoxyacetyl
6	benzoyl
7	methyloxaloyl
8	pivaloyl
9	trifluoracetyl
10	bromoacetyl
11	hydroxyacetyl
12	morpholinylacetyl
13	N,N-dimethylaminoacetyl
14	N-benzylaminoacetyl
15	N-phenylaminoacetyl
16	N-benzyl-N-methylaminoacetyl
17	N-methyl-N-(2-hydroxyethyl)aminoacetyl
18	N-methylcarbamoyl
19	3-methylbutyryl
20	N-isobutylcarbamoyl
21	succinoyl (3-carboxypropionyl)
22	carbamoyl
23	N-(2-indanyl)aminoacetyl

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TABLE 13
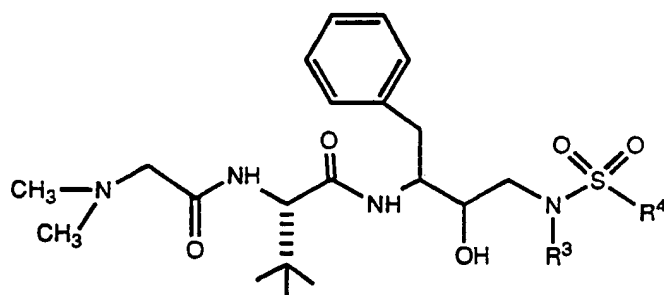
Entry	R^3	R^4
1	-CH3	-n-Butyl
2	-i-Butyl	-CH3
3	-i-Butyl	-n-Butyl
4	-i-Propyl	-n-Butyl
5	-C6H5	-n-Butyl
6	-CH2—(cyclohexyl)	-n-Butyl
7	-CH2—(phenyl)	-n-Butyl
8	(cyclohexyl)	-n-Butyl
9	-i-Butyl	-n-Propyl
10	-i-Butyl	-CH2CH(CH3)2
11	-(R)-CH(CH3)—(phenyl)	-n-Butyl
12	-CH2—(cyclohexyl)	-i-Propyl
13	-CH2—(cyclohexyl)	-CH2CH2CH(CH3)2
14	i-Butyl	-CH2CH3
15	i-Butyl	-CH(CH3)2
16	i-Butyl	(cyclohexyl)

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TABLE 13 (cont.)
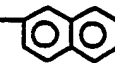
Entry	R³	R⁴
17	$-CH_2-$	$-(CH_2)_2CH(CH_3)_2$
18	$(CH_2)_2CH(CH_3)_2$	$-CH(CH_3)_2$
19	i-Butyl	$-CH(CH_3)_2$
20	i-Butyl	$-C(CH_3)_3$
21	$-CH_2$	$-C(CH_3)_3$
22	$-(CH_2)_2CH(CH_3)_2$	$-C(CH_3)_3$
23	$-CH_2C_6H_5$	$-C(CH_3)_3$
24	$-(CH_2)_2C_6H_5$	$-C(CH_3)_3$
25	n-Butyl	$-C(CH_3)_3$
26	n-Pentyl	$-C(CH_3)_3$
27	n-Hexyl	$-C(CH_3)_3$
28	$-CH_2-$	$-C(CH_3)_3$
29	$-CH_2C(CH_3)_3$	$-C(CH_3)_3$
30	$-CH_2CH_2-N$ O	$-C(CH_3)_3$
31	$-CH_2C_6H_5OCH_3$ (para)	$-C(CH_3)_3$
32	$-CH_2-$	$-C(CH_3)_3$
33	$-CH_2-$	$-C(CH_3)_3$
34	$-(CH_2)_2C(CH_3)_3$	$-C(CH_3)_3$
35	$-(CH_2)_4OH$	$-C(CH_3)_3$
36	$-CH_2-$ $-F$	$-C(CH_3)_3$

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TABLE 13 (cont.)
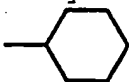
	Entry	R3	R4
5			
	37	-CH2-<pyridine>	-C(CH3)3
	38	-CH2CH(CH3)2	-C6H5
	39	i-amyl	-CH2C(CH3)3
	40	-<cyclohexyl>	-CH2C(CH3)3
10	41	CH3-<cyclohexyl>	-CH2C(CH3)3
	42	i-butyl	-CH2C(CH3)3
	43	-CH2Ph	-Ph
	44	-CH2-<phenyl>-F	-Ph
	45	-CH2-<cyclohexyl>	-Ph
15	46	-CH2-<phenyl>-OCH3	-Ph
	47	-CH2-<pyridine>N	-Ph
	48	-CH2-<cyclopropyl>	-Ph
	49	-CH2CH=CH2	-Ph
	50	-<phenyl>	-Ph
20	51	-<cyclohexyl>	-Ph
	52	-CH2CH2Ph	-Ph
	53	-CH2CH2CH2CH2OH	-Ph
	54	-CH2CH2N(CH3)2	-Ph
	55	-CH2CH2-N<morpholine>O	-Ph
25	56	-CH3	-Ph

TABLE 13 (cont.)
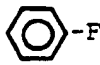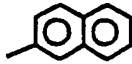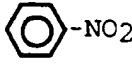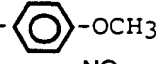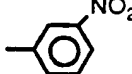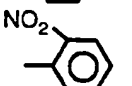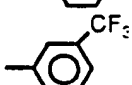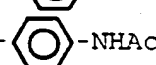
Entry	R^3	R^4
57	-CH$_2$CH$_2$CH$_2$SCH$_3$	-Ph
58	-CH$_2$CH$_2$CH$_2$S(O)$_2$CH$_3$	-Ph
59	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-phenyl
60	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-CH$_2$-phenyl
61	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-CH$_2$CH$_2$CH$_3$
62	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-CH$_3$
63	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-phenyl-F
64	-CH$_2$CH$_2$CH(CH$_3$)$_2$	methylnaphthyl
65	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-phenyl-NO$_2$
66	-CH$_2$CH$_2$CH(CH$_3$)$_2$	thienyl (S)
67	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-phenyl-OCH$_3$
68	-CH$_2$CH$_2$CH(CH$_3$)$_2$	phenyl-NO$_2$
69	-CH$_2$CH$_2$CH(CH$_3$)$_2$	NO$_2$-phenyl
70	-CH$_2$CH$_2$CH(CH$_3$)$_2$	CF$_3$-phenyl
71	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-phenyl-NHAc
72	-CH$_2$CH$_2$CH(CH$_3$)$_2$	-phenyl-Cl

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TABLE 13 (cont.)
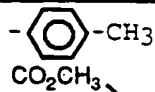
Entry	R³	R⁴
73	$-CH_2CH_2CH(CH_3)_2$	$-\bigcirc-CH_3$
74	$-CH_2CH_2CH(CH_3)_2$	CO_2CH_3 (phenyl)
75	$-CH_2CH(CH_3)_2$	$-\bigcirc$
76	$-CH_2CH(CH_3)_2$	$-\bigcirc-F$
77	$-CH_2CH(CH_3)_2$	$-\bigcirc-NHAc$
78	$-CH_2CH(CH_3)_2$	$-\bigcirc-CH_3$
79	$-CH_2CH_2CH_3$	$-\bigcirc-OCH_3$
80	$-CH_2CH_2CH_2CH_3$	$-\bigcirc-OCH_3$
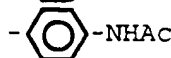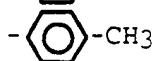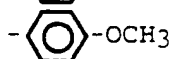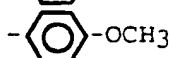
a benzyloxycarbonyl
b 2-quinolinylcarbonyl

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Table 14
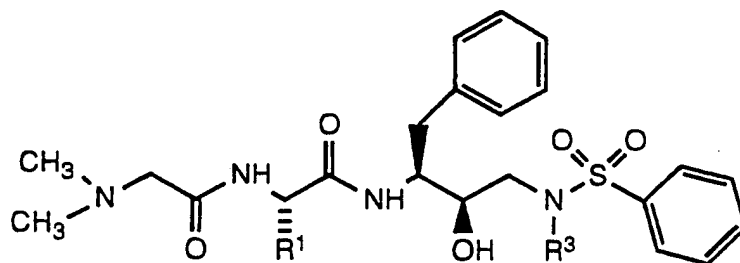
Entry	R^1	R^3
1	$C(CH_3)_3$	$CH_2CH_2CH(CH_3)_2$
2	$CH_2C \equiv CH$	$CH_2CH_2CH(CH_3)_2$
3	$C(CH_3)_2(SCH_3)$	$CH_2CH_2CH(CH_3)_2$
4	$C(CH_3)_2(S[O]CH_3)$	$CH_2CH_2CH(CH_3)_2$
5	$C(CH_3)_2(S[O]_2CH_3)$	$CH_2CH_2CH(CH_3)_2$
6	$C(CH_3)_3$	$CH_2CH(CH_3)_2$
7	$C(CH_3)_3$	cyclohexyl
8	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$
9	$CH(CH_2CH_3)(CH_3)$	$CH_2CH(CH_3)_2$

Table 14A
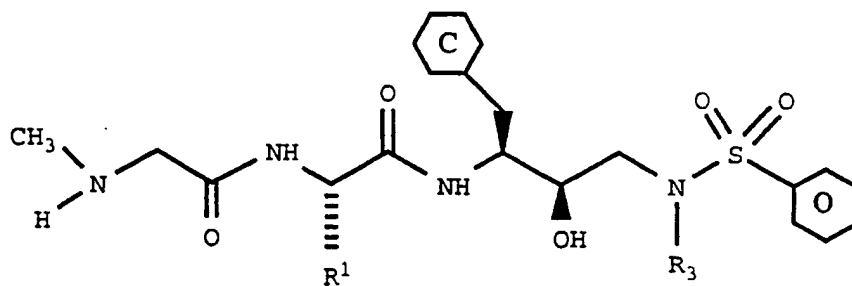
Entry	R^1	R^3
1	$C(CH_3)SCH_3$	$CH_2CH_2CH(CH_3)_2$

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Table 15

R=CH₃, H

5

Ar

10

Table 16

R₁	R₈	R₁	R₈
(2-piperidinyl-pyridin-5-yl)methoxy	H or CH₃	(5-methyl-pyridin-3-yl)methoxy	H or CH₃
(2-morpholinyl-pyridin-5-yl)methoxy	H or CH₃	(4-methyl-pyridin-3-yl)methoxy	H or CH₃
(2-(4-methylpiperazin-1-yl)-pyridin-5-yl)methoxy	H or CH₃	(4-methyl-thiazol-5-yl)methoxy	H or CH₃
(2-piperazin-1-yl-pyridin-5-yl)methoxy	H or CH₃	(2-methyl-thiazol-5-yl)methoxy	H or CH₃
(2-pyrrolidin-1-yl-pyridin-5-yl)methoxy	H or CH₃	(2-amino-thiazol-5-yl)methoxy	H or CH₃
(2-(methylamino)-pyridin-5-yl)methoxy	H or CH₃	(2-methyl-pyridin-3-yl)methoxy	H or CH₃
(2-(dimethylamino)-pyridin-5-yl)methoxy	H or CH₃	(6-methyl-pyridin-3-yl)methoxy	H or CH₃
(furan-3-yl)methoxy	H or CH₃	(thiazol-5-yl)methoxy	H or CH₃
(furan-2-yl)methoxy	H or CH₃		

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Table 16A

5

R

10

Table 16B

5

R

H_2N

CH_3

CH_3

OH

OH

H_2N CH_3

H_2N CH_3

HO CH_3

NH_2 CH_3

CH_3 CH_3

10